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*Blood Pressure; Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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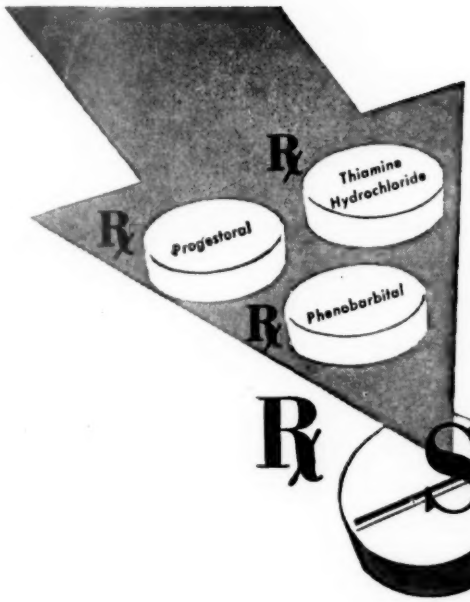

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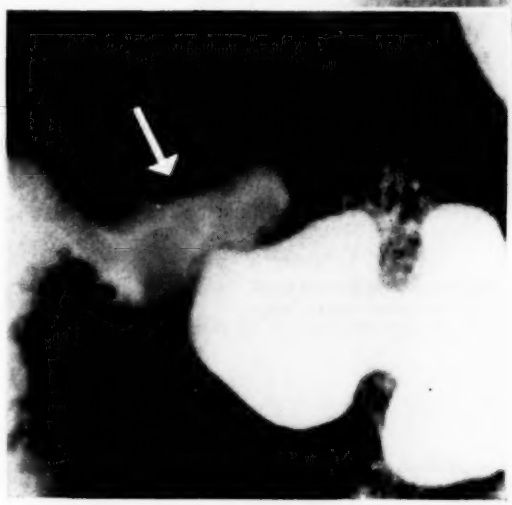

Top left: "X-rays revealed a huge ulcer crater in the duodenal bulb."

Top right: "Twelve days later the crater was strikingly reduced in size."

Bottom: "Two weeks later another spot roentgenogram revealed complete healing."

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ORIGINAL ARTICLES

MECHANICAL PRODUCTION OF EXPIRATORY FLOW RATES SURPASSING THE CAPACITY OF HUMAN COUGHING*†

By Alvan L. Barach, M.D.

CLINICAL PROFESSOR OF MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY; ASSOCIATE ATTENDING PHYSICIAN, PRESBYTERIAN HOSPITAL

Gustav J. Beck, M.D.

ASSISTANT IN MEDICINE, PRESBYTERIAN HOSPITAL

AND

William Smith

TECHNICAL ASSISTANT

(From the Department of Medicine, Columbia University, College of Physicians and Surgeons and the Presbyterian Hospital, New York, New York)

Physical methods which produced effects similar to human coughing were developed as an aid to the elimination of bronchial secretions in clinical entities in which retention of mucopurulent exudate resulted in pulmonary atelectasis or impaired respiratory function, including poliomyelitis, myasthenia gravis, bronchial asthma, bronchiectasis and pulmonary emphysema[2,3,4]. Further investigation of the physiologic changes induced by coughing led to the development of a more effective physical technique by which expiratory flow rates were produced that surpassed those attainable by the most vigorous cough of normal individuals as well as patients with bronchopulmonary disease.

The first methods employed that initiated pressure changes in the respiratory tract comparable to those found in coughing consisted of a modification of explosive decompression. With the body of the patient totally enclosed in a steel chamber, a pressure drop of 1/7th of an atmosphere was induced in 0.06 second at the start of the expiratory cycle; a close-fitting baffle placed around the neck of the patient provided a differential chest compressing pressure of 30 to 40 mm. Hg at the start of the expiratory cycle. This mechanical "cough" chamber was made by adapting the equalizing pressure chamber, originally developed to immobilize the lungs of patients with pulmonary tuberculosis, for the pur-

* This study was supported by a grant from the National Foundation for Infantile Paralysis.
† Presented at the Meeting of the Association of American Physicians at Atlantic City, New Jersey, May 5-6, 1953.

pose described. The second method utilized the relaxation pressure of fully inflated lungs, produced by an intratank negative pressure of 40 mm. Hg in the conventional respirator, with the patient's head in the outer atmosphere. Termination of the pressure surrounding the body in 0.04 second permitted the elastic recoil of the lungs and surrounding structures to empty a high tidal volume swiftly, without opposition from the gradually decreasing negative pressure characteristic of other forms of intermittent pressure breathing. The expiratory flow rates at the start of the expiratory cycle produced by this process, called exsufflation, were found to be approximately 60% as high as the maximal flow rates of the most vigorous coughs of a series of normal individuals and generally higher than those of patients with poliomyelitis who had breathing difficulties[3,4]. Another physical technique employed was a combination of exsufflation plus either (a) manual (positive pressure) compression of the chest or (b) the application of a negative pressure of 20 mm. Hg to the upper respiratory passageway during the expiratory cycle, in a dome surrounding the head of the patient, with an intra-dome pressure of minus 20 mm. Hg[3,5]. The gradient of pressure from the alveoli to the outer atmosphere was thus increased and, when the pressure in the body compartment became atmospheric and the pressure in the dome surrounding the head was maintained at minus 20 mm. Hg, a compressing chest pressure of 20 mm. Hg was achieved. Although the therapeutic value of exsufflation plus negative intra-dome pressure was apparent as an effective clinical method of eliminating previously retained bronchial secretions, the precise initiation of the pressure changes described, as well as their measurement, presented technical difficulties when the body and head of the patient were both totally enclosed in the respirator.

The purpose of this paper is to describe a mechanism by which negative pressure is applied to the upper respiratory passageway (by a mask or mouthpiece) at the moment the peak inspiratory pressure is reached. With the use of a high-speed suction blower, expiratory flow rates were readily produced beyond the capacity of human coughing. At the start of application of negative pressure, the diameter of the bronchial tree is at its widest. The efficiency of the expiratory blast of air responsible for elimination of secretions from the lungs seemed to be largely dependent on aeration of alveoli previously poorly ventilated because of obstructing mucous plugs[3,4,5,8,9].

Method. The E.W.N.P. device (exsufflation with negative pressure) includes a blower to inflate the lungs gradually with the positive pressure desired, that is, 20 to 40 mm. Hg, and an additional blower which develops a negative pressure of 20 to 40 mm. Hg, with high volume flow rates; the latter may be increased by a setting on a Variac to 15 or more liters per second, or twice the air velocity of the cough of most healthy individuals. A valving arrangement is connected by rubber tubing to the positive and negative pressure outlets of the blower and the mask (or mouthpiece). The lungs are slowly inflated by air from the positive pressure blower and, at the peak inspiratory pressure, the patient (or attendant) pulls a trigger which opens the valve to the negative pressure blower. The inspiratory pressure may also be terminated in 2.5 seconds by a solenoid valve operated by a time-delay relay circuit, as illustrated in Fig. 1.* The increased pressure gradient established between the pressure of the inflated lungs and the negative pressure maintained in the mask is responsible for air being expelled from the lungs at a flow rate greater than that previously obtained in maximal human coughing.

* The two models of the E.W.N.P. apparatus are manufactured by the O.E.M. Corporation, East Norwalk, Connecticut. The Exsufflator used as an attachment to the conventional tank respirator is made by the De Florez Company, New York.

Results. The rapidity of the mask pressure drop is shown in Fig. 2, in which it will be seen that a peak inspiratory pressure of 33 mm. Hg falls to 6 mm. Hg below the atmosphere in 0.02 second, and is then succeeded by a further subatmospheric drop of 22 mm. Hg.

The expiratory volume flow rates in maximal human coughing were computed from the differential pressure across a ½ inch orifice in a ¾ inch metal tube by a Statham strain gauge. The relationship between the differential pressure and air flow rates, measured by means of a variable-speed motor

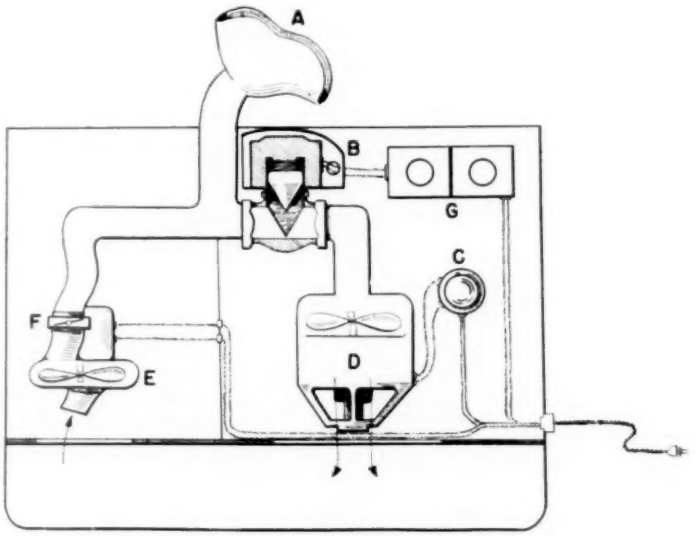

Fig. 1. – During inspiration, the mask (A), is connected to a pressure-blower (E), by which inflation of the lungs is accomplished. The duration of inspiration, generally 2.5 seconds, is regulated by one of a pair of time-delay switches (G), activating a solenoid (B). At the peak of inspiration, the solenoid (B) opens, connecting the mask (A), to the negative pressure-blower (D). The peak positive and negative pressures may be varied by means of a butterfly valve (F), and a powerstat (C), respectively.

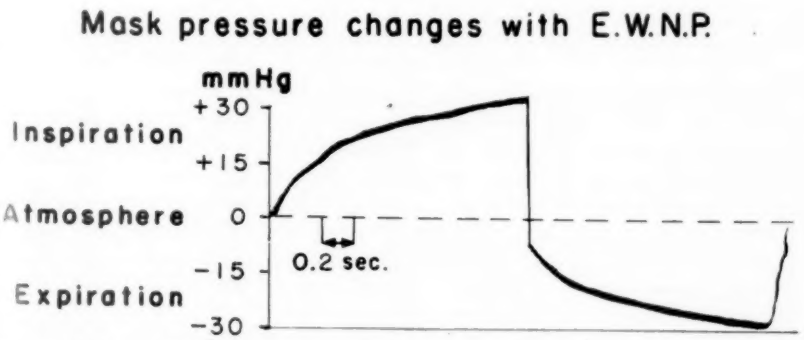

Fig. 2. – The peak mask pressure of 36 mm. Hg is developed slowly. The opening of a solenoid valve initiates expiration, the pressure dropping from 36 mm. Hg to the atmosphere and 38 mm. Hg below the atmosphere, a total of 74 mm. Hg.

blowing into a Tissot spirometer, was perfectly linear. The average maximum expiratory volume flow rates in 15 normal subjects tested with E.W.N.P. were 15% higher than those obtained by their most powerful coughs; in 9 of 20 patients with respiratory difficulties, bronchial asthma, pulmonary emphysema, bronchiectasis or poliomyelitis, the maximal expiratory flow rates were less than 3000 cc.; the calibration of the flowmeter on a Statham strain gauge is not accurate with flows under 3000 cc./sec. The average flow rates produced by E.W.N.P. were at least twice those initiated by their maximal coughs, as seen in Table 1. The individual results are shown in Table 1.

TABLE 1.—PEAK EXPIRATORY FLOW RATES DURING A COUGH OF MAXIMAL EFFORT AND DURING E.W.N.P., IN PATIENTS WITH BRONCHIAL ASTHMA, PULMONARY EMPHYSEMA, BRONCHIECTASIS AND CHRONIC SPINAL POLIOMYELITIS.

A. Normal Subjects

Case No.	Diagnosis	Cough cc./sec.	E.W.N.P. cc./sec.	$\frac{E.W.N.P.}{Cough} \times 100$ Per Cent
1.		5380	7820	145
2.		8360	9040	108
3.		5380	7820	145
4.		10670	9040	85
5.		4570	6200	136
6.		9580	9450	97
7.		6200	6600	106
8.		5110	5790	113
9.		6060	6060	100
10.		9310	7550	81
11.		8230	9450	115
12.		8640	10530	122
13.		9850	11480	117
14.		9850	11480	117
15.		9180	10530	115
	Average			115

B. Patients with Bronchial Asthma, Pulmonary Emphysema Bronchiectasis and Chronic Spinal Poliomyelitis

1.	Pulmonary emphysema	<3000	7280	243
2.	Pulmonary emphysema	<3000	8910	297
3.	Bronchiectasis	7820	9450	121
4.	Pulmonary emphysema and Bronchial asthma	<3000	6200	207
5.	Pulmonary emphysema	5790	8230	142
6.	Pulmonary emphysema	<3000	10400	347
7.	Chronic spinal polio	<3000	10960	366
8.	Pulmonary emphysema	5790	7420	128
9.	Bronchial asthma	5790	8500	147
10.	Pulmonary emphysema	<3000	7960	265
11.	Pulmonary emphysema	4570	7820	171
12.	Bronchial asthma	4980	5790	116
13.	Pulmonary emphysema	<3000	6800	227
14.	Pulmonary emphysema	<3000	6870	229
15.	Bronchial asthma	5930	8230	138
16.	Bronchial asthma	4570	5790	127
17.	Bronchiectasis	4430	6200	140
18.	Pulmonary emphysema	3620	5790	160
19.	Bronchial asthma	<3000	5520	184
20.	Bronchial asthma	3620	4300	119
	Average			194

The maximal expiratory flow rate of one normal subject during a most vigorous cough, 9800 cc. per second and during E.W.N.P. 10,800 cc. per second, is illustrated in Fig. 3.* A graphic record of a cough of maximal effort in a patient with pulmonary emphysema is shown in Fig. 4, in which it is seen that the maximal expiratory flow rate was 3000 cc./sec. (or less), as compared to a flow rate of 8910 cc./sec. with

tor responsible for the difficulty of eliminating secretions by a cough in patients with chronic pulmonary disease is a decreased tidal volume; in a bronchospirometric study of the quantity of air expelled by each lung by a voluntary cough Vaccarezza and his colleagues showed that the affected lung of patients with chronic pulmonary tuberculosis expelled one-fourth as much air as the normal lung[13].

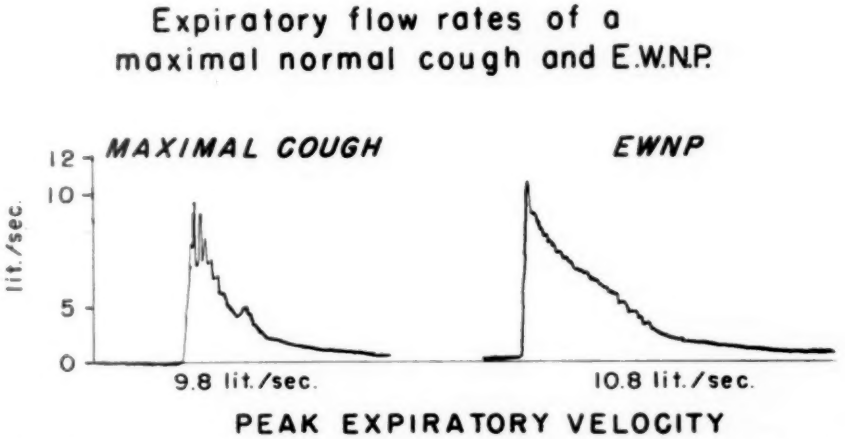

Fig. 3. – The pneumotachograph record indicates an expiratory volume flow rate of 9.8 liters per second during a cough of maximal effort in a healthy individual. The expiratory volume flow rate mechanically produced by E.W.N.P. was similar in general contour but significantly higher, namely, 10.8 liters per second.

E. W. N. P. A similar record in a patient with poliomyelitis is shown in Fig. 5, in which a cough of maximal effort revealed a flow rate of 3000 cc./sec. (or less), whereas expiration with E. W. N. P. manifested a flow rate of 10,960 cc./sec. In patients with pulmonary emphysema and severe bronchial asthma collapse of the bronchi may take place during the cough as result of a relative increase in intra-alveolar pressure[1,10,11,12]. Another factor

Inflation of the chest is accomplished by a *gradual* increase in pressure to prevent the occurrence of high velocities which would tend to blow secretions into the lungs. At the peak inspiratory pressure, the bronchi are markedly dilated, which facilitates the passage of air beyond occluding plugs into the alveoli and thereby enhances the physiological effect of the subsequent mechanically induced high volume flow rate in expiration. Since

*This record was obtained by Dr. James L. Whittenberger and Dr. Jere Mead with the use of a monel screen and their pneumo-tachograph. The authors wish to express their appreciation for this as well as many other similar records which were made during a visit of one of us (G.B.) to their laboratory.

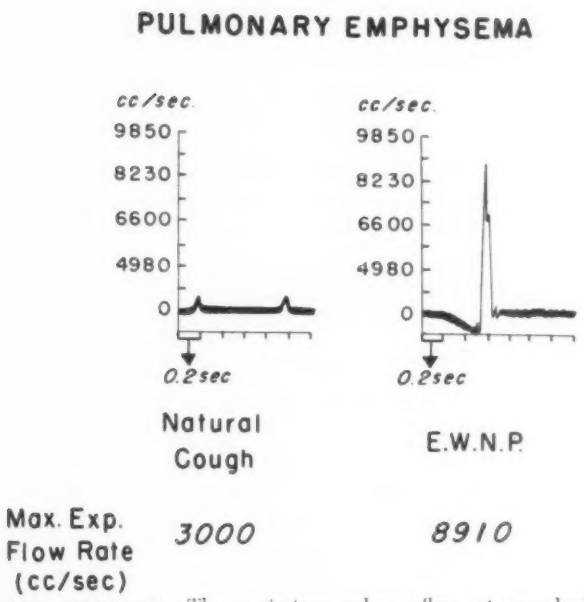

Fig. 4. — PULMONARY EMPHYSEMA. The expiratory volume flow-rate reached a maximum of 8910 cc./sec. when expiration was accomplished with E.W.N.P. In contrast, the expiratory volume flow-rate was 3000 cc./sec. (or less), during a maximal cough.

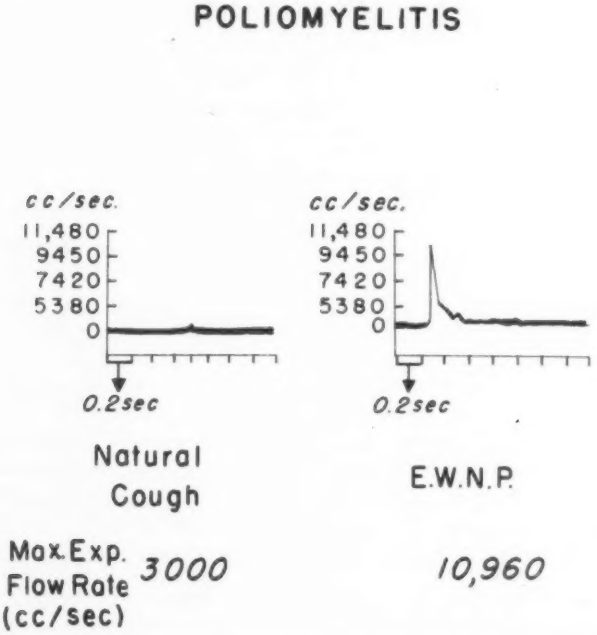

Fig. 5. — POLIOMYELITIS. The maximal expiratory flow-rate when expiration was accomplished by E.W.N.P., was 10,960 cc./sec., whereas the maximal natural cough of this patient was accompanied by a flow rate of 3000 cc./sec. (or less).

the volume flow rates may be altered by physical means to equal or surpass the air velocities of human coughing, the utilization of air blast, that is, high air pressure and velocity, may be used on a wide range to facilitate the removal of mucoid and purulent sputum from the lungs.

The effectiveness of expiratory flow rates of this order of magnitude on removal of foreign bodies from the lungs of anesthetized dogs was revealed by an investigation by Bickerman[7]. Metal objects, including lead balls, screws, and safety-pins, inserted by a bronchoscope into the lower bronchi were eliminated by 6 to 12 exsufflations with negative pressure. The lead balls used in this study weighed 0.6 gm. and were 4.5 mm. in diameter. The lung inflating pressure employed was 30 mm. Hg and the negative pressure 40 mm. Hg.

The nature of the clinical results achieved by the physical methods previously employed has recently been reported[3]. The technique presented in this paper, E. W. N. P., appears to have a superior effectiveness over exsufflation without negative pressure. The clinical results of the use of this procedure will be briefly summarized. Elimination of bronchial secretions was followed by clearing of pulmonary atelectasis in 8 patients who manifested this condition as a complication of either poliomyelitis (5 cases), spinal or chest injuries (2 cases), and bronchial asthma (1 case). Of a combined group of 40 patients with pulmonary emphysema and chronic bronchitis, bronchial asthma and bronchiectasis, 30 manifested clinical improvement of varying degree as result of mechanical elimination of bronchial secretions. No significant benefit was observed in one patient with poliomyelitis, 4 patients with pulmonary emphysema or pulmonary fibrosis, and 5 patients with bronchial asthma. The clinical effects and methods of treatment will be reported in full later, but it may be pointed out that the value of elimination of retained secretions from the lungs depends upon a variety of factors, including particularly the extent to which mucoid and mucopurulent sputum within the bronchial tree is a handicap to respiratory function.

Summary. The mechanical production of expiratory flow rates surpassing those recorded in maximal human coughing has been achieved by exsufflation with negative pressure; this procedure consists of inflation of the lungs by a gradual increase of pressure from a positive pressure blower; at the peak inspiratory pressure of 20 to 40 mm. Hg, the operation of a valve connects the upper respiratory passageway (by mask or mouthpiece) to the negative side of a vacuum blower, by which the peak pressure drops below that of the atmosphere in 0.02 second.* Expiratory volume flow rates of 10,000 cc. per second have been produced by E.W.N.P. in normal individuals and patients with respiratory difficulties. The average expiratory flow rate initiated by the portable apparatus employed was 15% higher than that produced by a cough of maximal effort in 15 normal individuals, and approximately double that of 20 patients with bronchial asthma, pulmonary emphysema, bronchiectasis or poliomyelitis. In the latter clinical entities, the use of E.W.N.P. was generally of therapeutic value in cases in which retention of bronchial secretions was the cause of pulmonary atelectasis or impairment of respiratory function.

* The negative pressure attained may be varied in degree and duration; in some apparatus a peak inspiratory pressure of 40 mm. Hg falls to minus 40 mm. Hg in 0.02 second.

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ARTERIAL HYPERTENSION: THE THERAPEUTIC EFFECT OF SODIUM RESTRICTION COMBINED WITH 1-HYDRAZINOPHTHALAZINE OR DIBENZYLINE

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It is now well established that sufficient restriction of dietary sodium will lower the blood pressure in a significant number of patients with arterial hypertension[1,3,4] and that this effect may be abetted by the use of cation exchange resins in conjunction with low sodium diets[5,7,8].

The purpose of the present study was to determine whether or not dietary sodium restriction combined with some of the newer hypotensive drugs would prove to be of more value in the treatment of arterial hypertension than either regimen used alone. 1-Hydrazinophthalazine (Apresoline) and N-phenoxy-isopropyl-N-Benzyl-B-Chloroethylamine (Dibenzyline, SKF 688A), an adrenergic blocking agent, were the drugs chosen for the investigation.

Apresoline Study. Fifteen ambulatory outpatients were used in this phase of the study and had, for the most part, been treated with low sodium diets and cation exchange resins and, with 2 exceptions, had obtained only a modest drop in blood pressure. They ranged in age from 36 to 59 years, averaging 47 years and from Grades I to III of the Keith, Wagener and Barker classification[10] and from Grades I to III in the Smithwick classification[14]. Before combined therapy, all had a diastolic blood pressure persistently at or above 100 mm. of mercury; none had azotemia; all had at least moderately good renal function as indicated by the common clinical tests: these being the criteria for their inclusion in the original low sodium-resin therapy group[7]. Blood pressures were recorded in the sitting, and, after 2 minutes in the standing position, at the start of each interview, and again after 10 or 15 minutes of relaxation and casual conversation with the physician. The lowest blood pressure of 5 determinations was recorded. Baseline and follow-up studies included electrocardiogram, funduscopic examination by one ophthalmologist, teleroentgenogram, ballistocardiogram, urinalysis, phenolsulfonphthalein excretion test, dilution-concentration test, blood urea nitrogen determination, complete blood count, 24-hour urine sodium determination frequently and, in some cases, urea clearance tests, intravenous urograms, urine cultures, sodium amytal and cold pressor tests and tests to rule

TABLE 1.—RESULTS OF LOW SODIUM DIET AND RESIN THERAPY COMBINED

Case No., Initials (Sex, Age)	†Smithwick Grade	With Apresoline: Mean Blood Pressure*: Control	Low Na, Resin Rx	Low Na, Resin and Apresoline Rx	Apresoline Rx only	Mean Blood Pressure Change from Control: Resin only	Resin and Apresoline	Apresoline only	Apresoline Dose per day	
1. L. D. (F. 55)	3	200	200	148	198	—0	—52	—2	400	
		124	115	91	116	—9	—33	—8		
2. I. H. (F. 41)	2	182	163	159	197	—15	—23	+15	200	
		123	117	103	127	—6	—20	+4		
3. J. B. (F. 48)	1	184	170	142	200	—14	—42	+14	400	
		122	117	107	130	—5	—15	+8		
4. T. B. (F. 36)	3	202	179	163	....	—23	—39	....	100	Avg. 214
		131	127	101	....	—4	—30	....		
5. F. D. (F. 45)	1	160	151	149	163	—3	—11	+3	150	
		120	117	105	118	—3	—15	—2		
6. D. S. (M. 51)	2	224	192	185	....	—32	—39	....	100	
		135	111	100	....	—24	—35	....		
7. E. G. (F. 59)	1	190	192	179	195	+2	—11	+5	150	
		100	97	85	100	—3	—15	0		
8. M. D. (F. 53)	3	240	231	214	....	—9	—26	....	400	
		137	128	121	....	—9	—16	....		
9. L. H. (F. 38)	2	199	199	184	200	—0	—15	+1	500	
		114	104	101	120	—10	—13	+6		
10. E. W. (F. 36)	2	205	180	187	....	—25	—18	....	400	Avg. 360
		132	123	123	....	—9	—9	....		
I (F. 59)	2	200	177	173	185	—23	—27	—15	400	
		110	90	90	90	—20	—20	—20		
12. E. M. (F. 44)	2	191	....	149	149	....	—42	—42	100	
		108	....	95	94	....	—14	—14		
13. A. H. (F. 45) 14. A. D. (F. 49) 15. R. P. (M. 50)	Could not tolerate Apresoline								Avg. Dose 275 mg. (q d.)	

* Blood pressures recorded in sitting position.
† At start of combined therapy.

out pheochromocytoma. Each patient had a complete history recorded and physical examination performed.

The diets prescribed contained 1 gm. of sodium used in conjunction with 45 gm. daily of the cation exchange resin Resodec or 48 gm. daily of Carbo-Resin taken after meals, the goal being to reduce the sodium level in the urine to less than 0.5 gm. per 24 hours, as previously reported[5,7]. These were supplemented by potassium citrate 1 gm. and calcium lactate 0.6 gm. in cherry syrup daily taken a few hours from the time of resin administration. The depressor drugs were given before meals. The duration of combined therapy was 2½ to 10 months, of low sodium-resin therapy 4 to 12 months, of depressor drug therapy alone 1 to 3 months, of initial control periods at least 3 months with some records extending back for several years, and of resin placebo periods 1 to 3 months. In all but one patient (Case 12), low sodium-resin therapy was given initially, after which Apresoline was administered. In some cases a second course of combined therapy was instituted if it appeared to have been of real value previously. Apresoline doses were begun at 75 mg. daily and gradually increased to the point of effectiveness or intolerance.

TABLE 2.—RESULTS WITH APRESOLINE AND LOW SODIUM DIETS IN CONJUNCTION WITH CATION EXCHANGE RESIN

(12 CASES)

	Diastolic Drop of 20 or more	*Diastolic Drop of 20 or more and to 100 or less*	*Systolic Drop of 25 or more*
Sodium Restriction with Resin	2	1	2
Sodium Restriction with Resin plus Apresoline	5	3	7
Apresoline only (7 cases)	1	1	1

RESULTS (TABLES 1 AND 2). Seven patients were carried through the complete cycle of therapies (Cases 1, 2, 3, 5, 7, 9, 11). Five went through two-thirds of the cycle. Three were unable to tolerate Apresoline and are excluded from the analysis.

Seven patients had at least a 10 mm. of mercury decrement of mean diastolic blood pressure below that reached with low-sodium-resin therapy alone and also at least a 15 mm. of mercury drop in diastolic pressure below the control level after Apresoline was added to their low sodium-resin program. Five had 20 or more points of diastolic pressure lowering on the combined program while only 2 attained this level without Apresoline. Two patients attained a systolic pressure lowering of 25 mm. or more while receiving low sodium-resin alone, one while receiving Apresoline alone and 7 while receiving combined therapy. Also all these added benefits from combined therapy were lost when the resin was stopped or salt added to the diet except for Case 11 who maintained her diastolic lowering. In the 7 who had substantial diastolic pressure decrements following the addition of Apresoline to their low sodium programs, the daily doses of Apresoline ranged from 100 to 400 mg., averaging 214 mg., a level lower than that reported to be usual when Apresoline is used alone[13,15].

The other 5 cases (8 through 12) did not show greater lessening of diastolic pressure after the addition of Apreso-

* Blood pressures recorded in sitting position
† At start of combined therapy.

15. R. P. (M. 50)

line to their low-sodium programs, despite the fact that higher daily doses (range 100 to 500 mg.; average 360) were used.

There were no appreciable postural blood pressure effects noted after the addition of Apresoline.

Illustrative Case. (Fig. 1). L. D., a 55-year-old Negro female housewife had had known hypertension for several years, and was hospitalized in September 1951, with congestive heart failure, manifested by dyspnea on mild exertion, orthopnea, cough, palpitations, ankle edema and lack of vigor. She was treated with digitalis, low-salt diet and bed rest. Studies revealed a 50% enlargement of the transverse cardiac diameter after digitalization, urine containing a trace of albumin and with a dilution-concentration range of 1.005 to 1.015, Grade II hypertensive and sclerotic changes in the ocular fundi, a blood urea nitrogen level of 15 mg. per 100 cc., a phenolsulphonphthalein test showing 23% excretion in 20 minutes and 63% excretion in 2 hours, abnormal ST-T changes in the electrocardiogram and an abnormal ballistocardiogram. Upon discharge in October 1951, cation exchange resin was added to her therapeutic regimen, her dietary prescription allowed 1 gm. of sodium per day, and potassium citrate, 1 gm., and calcium lactate, 0.6 gm., were given daily. During the ensuing 5 months there was little change in her blood pressure, but she stayed out of congestive failure, the transverse cardiac diameter decreased to 20% enlargement, the ballistocardiographic pattern improved and the other studies were essentially as before. In April 1952, Apresoline was added to her program, eventually reaching a daily dose of 400 mg. The blood pressure gradually fell to normal levels and 3½ months later the heart size was found to be 17% enlarged, the electrocardiographic pattern was improved, the ballistocardiographic pattern was very much improved, the urine was free of albumin, there was 40% PSP excretion in 20 minutes and 70% in 2 hrs., the blood urea nitrogen was still normal and the fundi still showed Grade II changes.

At this point the cation exchange resin was discontinued and the patient was carried on 400 mg. Apresoline daily and the same diet as before. This was accompanied by an increase in the blood pressure and an increased excretion of urine sodium. Headache soon returned and the patient gained 7 lbs. and became dyspneic. Upon resumption of combined therapy with both resin and Apresoline the blood pressure again dropped to innocent levels where it remains, and the symptoms again disappeared.

It is clear that in this case neither sodium restriction nor Apresoline alone can control the patient's blood pressure but that both together do it well.

SIDE REACTIONS AND COMPLICATIONS. The previously reported side reactions to Apresoline[13,15] were noted in some of these patients consisting of tachycardia, pounding of the heart, aching in the muscles, a tired pepless, drowsy feeling, dizziness, a sensation of tightness about the head and headache. One patient developed a maculopapular skin rash within one week of starting Apresoline. He also developed practically all of the above complaints and the drug had to be stopped. These symptoms were severe enough to necessitate cessation of therapy in 3 of the 15 patients and they are omitted from the series analysis. The occurrence of side reactions was fairly common in the remainder of the group, but were fairly well controlled by Dramamine, and passed off in 2 to 4 weeks. None of the patients had initially, or developed later, any signs of coronary, renal or cerebrovascular insufficiency and none died.

LABORATORY STUDIES. The baseline studies have been at least partially repeated so far in 8 of the cases following 4 to 10 months on the combined therapy program and the results are depicted in Table 3. The heart size remains unchanged in 8 patients; in 7 the electrocardiogram is unchanged, in 1 it improved, and it is worse in none; the fundi are the same in 5, better in 2, and worse in 1 (more spasm of the arterioles); the phenolsulfonphthalein excretion is the same in 1, better in 3 and worse in 1; the urinalysis is the same in 6, better in 1 and worse in 1; the blood urea nitrogen remains normal in all 8; and the ballistocardiogram is

better in 2 and worse in 1 patient. Blood counts have not changed significantly.

COMMENT. It would appear that the combination of low sodium and Apresoline therapy increases the number of patients with essential hypertension who may achieve a lowering of blood pressure by medical means, where either type of therapy used alone does not accomplish this. It seems logical that this effect should occur since one

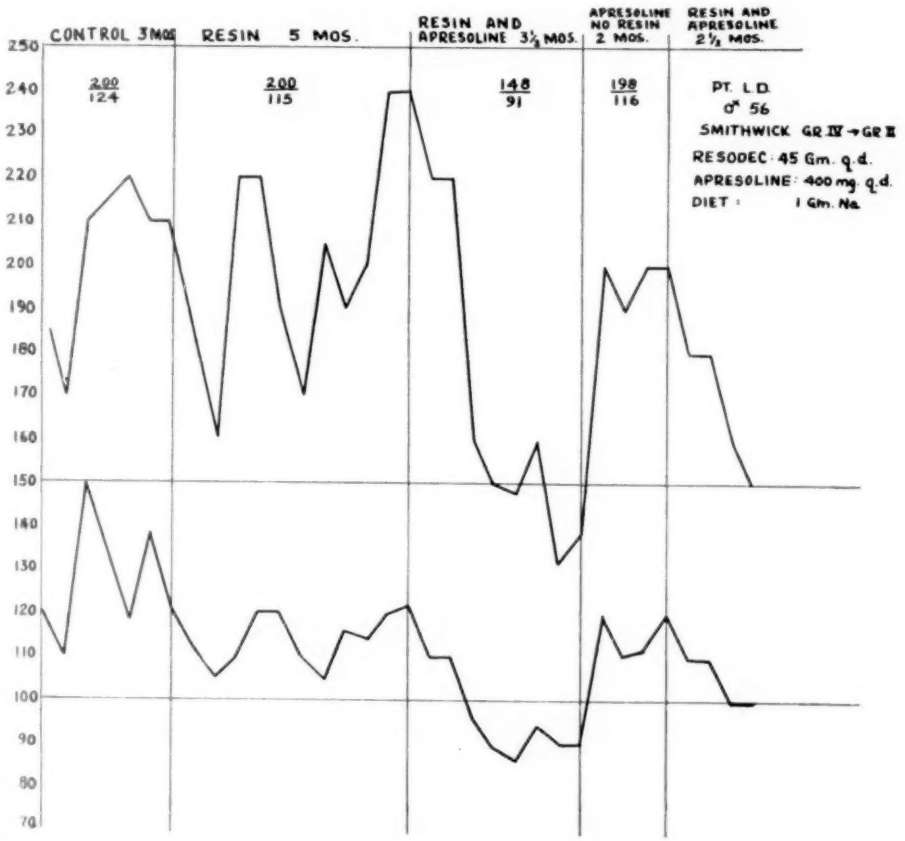

Fig. 1.—Blood pressure record of patient L.D. during control and indicated treatment periods, respectively.

TABLE 3.—CHANGES FOLLOWING COMBINED THERAPY OF ESSENTIAL HYPERTENSION WITH LOW SODIUM-CATION EXCHANGE RESIN AND APRESOLINE

(AFTER 2½ TO 10 MONTHS OF TREATMENT)*

	Heart Size	*EKG*	*BKG*	*Fundi*	*PSP*	*Urine*	*BUN*
Improved	0	1	2	2	3	1	0
Same	8	7	0	5	1	6	8
Worse	0	0	1	1	1	1	0

* Responses do not correlate well with blood pressure responses.

TABLE 4.—RESULTS OF THERAPY OF HYPERTENSION WITH LOW SODIUM-CATION EXCHANGE RESIN AND DIBENZYLINE

Case No., Initials (Sex, Age)	†*Smith-wick Grade*	*Control BP*	*Resin BP*	*Resin 688.A BP*	*688.A BP*	*Mean* Blood Pressure Change from Control*			*Mean Standing BP*			*Daily Dose 688.A*
						Resin	*Resin and 688.A*	*688.A*	*Control*	*Resin and 688.A*	*688.A*	
1. D. S. (M. 51)	2	224	192	181	..	—32	—43	..	230	183	..	90
		135	111	101	..	—24	—34	..	145	118	..	
2. W. S. (M. 54)	1	187	160	152	177	—27	—35	—10	180	162	177	120
		113	99	93	110	—14	—20	—3	120	105	124	
3. L. G. (F. 52)	2	212	165	154	161	—47	—58	—51	210	146	164	120
		138	110	103	110	—28	—35	—28	146	114	111	
4. K. B. (F. 58)	2	200	191	150	164	—9	—50	—36	210	155	160	80
		102	91	79	84	—11	—23	—18	112	84	93	
5. N. D. (F. 51)	3	200	191	191	..	—9	—9	..	210	180	..	120
		116	100	93	..	—16	—23	..	126	99	..	
6. S. G. (F. 50)	2	235	187	160	..	—48	—75	..	220	160	..	50
		142	117	110	..	—25	—32	..	150	119	..	
7. R. B. (F. 54)	2	182	156	128	..	—26	—54	..	190	136	..	60
		130	107	92	..	—23	—37	..	138	100	..	
8. T. W. (M. 55)	2	216	189	152	..	—27	—64	..	192	155	..	130
		127	112	103	..	—15	—24	..	124	106	..	
9. M. W. (F. 60)	3	235	190	175	170	—45	—60	—65	240	160	160	40
		130	104	93	90	—26	—37	—40	140	90	94	
10. D. S. (M. 67)	2	195	190	155	..	—5	—40	..	220	196	..	100
		126	116	102	..	—10	—24	..	136	128	..	

11. E. P. (F. 43) 1	186	155	153	168	−31	−31	−18	180	149	165	40
	114	94	93	99	−20	−21	−15	114	98	103	
12. N. L. (F. 50) 1	203	172	180	160	−31	−23	−43	210	195	180	160
	117	99	112	100	−18	−5	−17	124	114	115	
13. M. D. (F. 53) 3	240	231	200	..	−9	−38	..	230	180	..	200
	137	128	123	..	−9	−14	..	147	126	..	
14. E. W. (F. 38) 2	205	180	178	..	−25	−27	..	220	199	..	60
	132	123	122	..	−9	−10	..	136	132	..	
15. E. R. (F. 51) 1	168	154	161	190	−14	−7	+22	170	146	165	60
	115	103	101	120	−12	−14	+5	120	106	115	
16. L. H. (F. 40) 2	199	199	197	..	−0	−2	..	206	189	..	300
	114	104	114	..	−10	−0	..	120	108	..	
17. M. J. (F. 48) 2	168	142	135	160	−26	−33	−8	154	168	168	30
	100	92	90	104	−8	−10	+4	106	84	110	
18. L. K. (F. 39) 1	190	184	150	179	−6	−40	−11	180	160	170	60
	115	115	107	115	−0	−8	−0	120	110	108	
19. J. G. (F. 55) 2	183	152	145	154	−31	−38	−29	180	140	150	80
	119	97	92	100	−22	−27	−19	120	105	105	
20. E. B. (M. 50) 4	190	220	225	..	+30	+35	..	200	203	..	80
	123	130	133	..	+7	+10	..	130	133	..	
21. A. L. (F. 51) 4	224	210	236	..	−14	+12	..	220	238	..	120
	136	138	123	..	+2	−13	..	150	130	..	

22–34: Could not tolerate **688**A

Avg.: 100 mg.

* B.P. recorded in sitting position
† At start of combined therapy

is attacking the hypertension with 2 means each of which has a different mechanism of action, it being thought that hypertension may be maintained by more than one mechanism[12]. Although the exact role of sodium in hypertension is not known there is some evidence that its depletion contributes to a decrease in peripheral vascular resistance[6,16], while the action of Apresoline seems to be as a neutralizer of a pressor substance elaborated by the midbrain and perhaps of other humoral agents[13,15].

Lower doses of Apresoline are required when used in conjunction with sodium restriction, an obvious advantage from the standpoint of reducing the incidence of side reactions and lessening expense to the patient. At present we do not feel that the sodium restriction can be any less rigid during combined therapy than when used alone.

Dibenzyline Study. Dibenzyline, (SKF 688A) is an adrenergic blocking agent affecting sympathetic stimuli peripherally at the nerve endings. It is related chemically to Dibenamine, but is active when given orally. Various reports so far have attributed to it very limited to moderate usefulness in the management of essential hypertension[2,9,11].

This phase of the investigation utilized 34 ambulatory outpatients studied in the same manner as described for the Apresoline group. Of these 21 were followed long enough for inclusion in the series. They ranged in age from 38 to 60 years, the average age being 51 years. In the Keith, Wagener and Barker classification[10] they ranged from Grades I to III, and in the Smithwick classification[14] from Grades I to IV, most of them falling into Grades II or III. Control periods were at least 3 months in duration, and many of the patients had been followed for several years. Most had received a placebo resin. All had previously been treated with sodium restriction and cation exchange resin for 4 to 12 months with moderate to no benefit before receiving Dibenzyline. Dibenzyline in the form of 10 mg. gelatin capsules was then added to the low sodium-resin regimen and this combined therapy was used for 2 to 6 months. After this, in many instances, the resin was stopped and Dibenzyline used alone. The latter procedure was not carried out invariably since, in some, there was obviously no extra benefit from the addition of Dibenzyline and therefore no point in going further with the study, and some of the other patients were lost to the follow-up before completing the full cycle of study.

TABLE 5.—RESULTS WITH DIBENZYLINE ALONE
(10 CASES)

* Diastolic blood pressure drop of 20 or more	2 (20%)
* Diastolic blood pressure drop of 20 or more and to 100 or less	1 (10%)
* Systolic blood pressure drop of 25 or more	5 (50%)
Prevention of Diastolic Increase in Standing Position	3 of 8

* Sitting position.

RESULTS. Of the 34 patients who were given Dibenzyline, 13 (38%) could not, or would not, take it long enough to permit evaluation of its hypotensive effect. Only 21 patients, therefore, were available for analysis. (Table 4.)

EFFECT OF DIBENZYLINE ALONE UPON THE BLOOD PRESSURE (Tables 4 and 5). Ten patients received Dibenzyline alone. Two of these had a mean dias-

tolic blood pressure drop of 20 mm. or more. One had both a mean diastolic drop of 20 mm. or more, and in addition, a drop to a level of 100 mm. or below. Five had a mean systolic pressure drop of 25 mm. or more. During the control period, 8 of the 10 showed a diastolic blood pressure rise of 5 mm. of mercury or more within 2 minutes after assuming the erect position. Dibenzyline prevented this occurrence or caused a fall in diastolic pressure in 3 of the 8. Sodium restriction had no appreciable effect upon this postural change.

Of the 10 patients who had a period of treatment on Dibenzyline alone, 8 had greater blood pressure reduction with the combination of sodium restriction and Dibenzyline; one had approximately the same blood pressure level with both programs (Case 9, Table 4); and another had a lower level of blood pressure with Dibenzyline alone than with combined therapy (Case 12, Table 4). It should be noted also that 9 of these 10 patients had about as good or better diastolic blood pressure drop from sodium restriction alone as from Dibenzyline alone, and with fewer side reactions (Cases 2, 3, 4, 11, 12, 15, 17, 18, 19, Table 4).

The daily dose levels of Dibenzyline ranged from 30 to 300 mg., averaging 100 mg., and were the same when used alone or in combination with sodium restriction. Dosage levels were started at 30 mg. daily and the maximum determined by blood pressure response or side reactions. The incidence and severity of the latter, to be discussed subsequently, were equally great whether Dibenzyline was used alone or in conjunction with sodium restriction.

EFFECT OF DIBENZYLINE COMBINED WITH LOW SODIUM-CATION EXCHANGE RESIN (Table 6). Of the 21 patients receiving combined therapy, 7 had previously achieved a drop in diastolic blood pressure of 20 mm. of mercury or more, but of this number only 2 had achieved also a drop in diastolic blood pressure level to 100 mm. or below with sodium restriction and exchange resins. The addition of Dibenzyline to this group increased the number achieving a drop in diastolic pressure of 20 mm. or more to 12 and the number achieving also a drop in diastolic pressure level to 100 mm. or below to 7. Five patients achieved at least a 10 mm. decrement in mean diastolic pressure level below that reached with low sodium-resin therapy by the addition of Dibenzyline.

With sodium restriction alone, 12 attained a systolic drop of 25 mm. or more. The addition of Dibenzyline increased this number to 15.

During the control period, 17 of the 21 patients, showed an increase in diastolic blood pressure of 5 mm. or more upon assuming the erect position.

TABLE 6.—RESULTS WITH DIBENZYLINE AND LOW SODIUM DIETS IN CONJUNCTION WITH CATION EXCHANGE RESINS

(21 CASES)

	*Diastolic Drop of 20 or more	*Diastolic Drop of 20 or more and to 100 or less	*Systolic Drop of 25 or more
Sodium Restriction with Resin	7	2	12
Sodium Restriction plus Dibenzyline with Resin	12	7	15

* Sitting position

During the period of sodium restriction and Dibenzyline therapy 13 showed this response. Table 7 shows a comparison of the results attained with sodium restriction by resin therapy alone, by Dibenzyline alone, and by both combined, in the 10 cases that were carried through the complete cycle of study. It is apparent that both sodium restriction alone or combined with Dibenzyline gives somewhat better results than does Dibenzyline alone.

enings were in the urinalysis (appearance of proteinuria), the phenolsulphonphthalein excretion and the ballistocardiogram. In the previously reported low sodium-resin series, the urinalysis was not adversely affected and the PSP excretion and ballistocardiographic pattern improved with greater frequency[5].

SIDE EFFECTS AND COMPLICATIONS OF DIBENZYLINE THERAPY. The gains made in controlling the blood pressure by adding Dibenzyline to sodium restric-

TABLE 7.—COMPARISON OF RESULTS WITH SODIUM RESTRICTION, DIBENZYLINE AND COMBINED SODIUM RESTRICTION-DIBENZYLINE THERAPIES

(CASES NO. 2, 3, 4, 9, 11, 12, 15, 17, 18, 19 OF TABLE 3)

	**Diastolic Pressure Drop of 20 or more*	**Diastolic Pressure Drop of 20 or more and to 100 or less*	**Systolic Pressure Drop of 25 or more*
Sodium Restriction	4	2	7
Sodium Restriction and Dibenzyline	6	5	8
Dibenzyline Only	2	1	5

* Sitting position

TABLE 8.—CHANGES OCCURRING AFTER 3 TO 5 MONTHS OF LOW SODIUM-EXCHANGE RESIN THERAPY COMBINED WITH DIBENZYLINE THERAPY

	Heart Size	*EKG*	*Fundi*	*PSP*	*Urine*	*BUN*	*BKG*
Better	2	1	4	3	0	0	1
Same	7	10	4	2	6	12	0
Worse	1	0	1	3	5	0	3
Totals	10	11	9	8	11	12	4

LABORATORY STUDIES. Baseline studies have been repeated in some of the group after 3 to 5 months of combined therapy and are depicted in Table 8. The degree of change attributable to each component of therapy cannot be assessed accurately, but previous studies with low sodium-cation exchange therapy in hypertension showed a better record of improvements (or at least lack of worsening) in the various areas studied than was found with the Dibenzyline treated patients in this series[5]. The most notable worstion, or by using it alone were not without significant cost to the patients. Side effects appeared in practically all patients and consisted of miosis with blurring of vision, dry mouth, nasal congestion, dizziness upon assuming the upright posture, drowsiness, aching in the muscles of the chest and neck, dyspnea on mild exertion, headache, tachycardia, "pounding of the heart", and a general vague feeling of being unwell. Most of these are really the result of the general adrenergic blocking action of the drug and not strictly

side effects, although the drowsiness, muscle aching and headache could be classed as such and have been noted by other authors[2,9,11]. These reactions caused the physician or the patient to discontinue therapy in 13 cases (38% of the original 34 patients), and caused frequent complaints from the remainder of the group. Most of the patients found the low sodium diet and cation exchange resins much preferable to the Dibenzyline. The side effects also prevented successful use of placebo medication because the patients quickly became aware of the change. One patient told of developing a hemiplegia during Dibenzyline therapy from which recovery was complete in 2 weeks although she continued to take the drug. Definite angina pectoris was noted in 2 patients, and 2 others died at home while receiving the drug, the symptoms suggesting myocardial infarction. Two hospital patients with malignant hypertension, (not included in this series) were given up to 500 mg. of Dibenzyline daily for several weeks with no effect whatsoever upon their blood pressure or upon the malignant course. Both died within 3 weeks of admission.

The undesirable concomitant signs and symptoms of Dibenzyline therapy were equally annoying whether it was being administered alone or with sodium restriction. Blood counts before and after Dibenzyline therapy showed no significant changes.

COMMENT. Dibenzyline appears to be of little value as a hypotensive agent when used alone, and, though somewhat effective when used with sodium restriction, the cost in side effects is great. Also there is a tendency for the blood pressure to fluctuate over a fairly wide range so that, while mean blood pressure changes may appear favorable, a chronological graph of the blood pressure is less impressive. Another disturbing effect is the tendency of the blood pressure to escape from control after 2 to 3 months of therapy even when the initial response has been good. Irreversible escape occurred in 5 patients and several others needed increased doses of the drug to remain in control. The conversion of a fairly steady blood pressure range into a widely fluctuating one, and the escape phenomenon have not been noted in 2 years experience with sodium restriction aided by the exchange resins.

These undesirable effects mitigate against widespread practical use of Dibenzyline in the therapy of hypertension, but, used in small doses and combined with other hypotensive drugs, it may find a useful niche.

A further practical consideration relative to the use of these drugs combined with sodium restriction is the need for extra vigilance in keeping patients faithfully on their low sodium diet since there seems to be a tendency, conscious or unconscious, toward less strict adherence when other medications are added.

Summary and Conclusions. (1) Apresoline combined with restriction of dietary sodium in conjunction with cation exchange resins is of value in obtaining a significant reduction of blood pressure and improvement in the cardiovascular and renal function in some patients with arterial hypertension where each of these agents used alone is of little or no value.

(2) Smaller doses of Apresoline may be used in this combined therapeutic program than are needed when the drug is administered alone.

(3) Dibenzyline, administered alone orally, is not a satisfactory agent for the treatment of arterial hypertension.

(4) In some patients Dibenzyline administered in conjunction with low-sodium-cation exchange resin therapy will cause an additional fall in blood pressure below that attained with

either type of therapy alone, but this gain is largely offset by the high incidence of undesirable reactions, and by the frequency of escape of the hypertension from the effect of the drug.

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HOMOLOGOUS SERUM-HEPATITIS FOLLOWING THE USE OF FRACTION IV PREPARED FROM POSTPARTUM PLASMA*

A report of four cases

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Although various fractions of human plasma have been shown to produce homologous serum hepatitis, Cohn's Fraction IV has never been incriminated. The present report records 4 cases apparently caused by this particular fraction which was prepared from pooled postpartum plasma.

Beneficial effects from the administration of pooled postpartum plasma in the treatment of rheumatoid arthritis have been reported by Granirer[5,6]. In his investigations plasma was collected 48 to 72 hours after delivery and pooled so that each lot represented plasma from 10 different women. By means of this material, he was able to induce sustained remissions in adults with rheumatoid arthritis for 3 weeks to 14 months following the cessation of therapy. Remission was characterized by an amelioration of joint symptoms, an improved sense of well being, a brighter mental outlook, increased appetite, gain in weight, improvement of anemia, and restoration of the albumin-globulin ratio to normal. No toxic effects were reported in 520 transfusions of postpartum plasma. Aronson[1] has reported similar findings in the treatment of rheumatoid arthritis using retroplacental plasma collected at the time of delivery.

The occurrence of homologous serum hepatitis following the use of whole blood[17], pooled plasma[3], and irradiated plasma[2,14,21] has been reported previously. In recent months investigations into the incidence of homologous serum hepatitis following administration of various fractions of human plasma have been published. Paine and Janeway[20] followed up 237 patients who received human albumin which had not been treated by irradiation and had been stored as dried plasma for a considerable time. After excluding those who died within 5 months after the infusion and those who had cirrhosis of the liver or other liver disease, there remained 33 who received albumin only and 93 who received blood or plasma in addition to albumin. No cases of serum hepatitis occurred in

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the former group. Since the albumin was prepared in lots of approximately 500 units of 25 gm. each, the number of donors represented in each unit is at least 2000. If the incidence of carriers is about 0.2%, it may be calculated that a single lot of albumin probably contains material from at least one infectious donor. The findings suggest that the use of human albumin does not carry the risk of homologous serum hepatitis that exists with the use of pooled plasma or even whole blood. Cockburn[4], in investigating an outbreak of homologous serum hepatitis in children given pooled plasma for measles prevention, found that 7 of 10 children who received a particular pool developed hepatitis. However, only 1 of 58 children given gamma globulin prepared from this same plasma pool developed the disease. He concludes that although gamma globulin may not be wholly free from the danger of transmitting homologous serum hepatitis, the risk is exceedingly small. These findings are in agreement with those of Janeway[15], Ordman[19], and Greenstein[7] who followed up patients given gamma globulin and found an extremely low incidence of hepatitis.

On the other hand, Janeway[16] has reported a 10% incidence of hepatitis among those receiving Cohn's Fraction I, which was distributed in the dry state and which cannot be treated after denaturation. Lesses[18] has reported 22 cases of homologous serum hepatitis following the use of human thrombin, which is derived from pooled plasma and directly prepared from Cohn's Fraction III-2.

During 1951, Cohn's Fraction IV prepared from pooled postpartum plasma was administered to a total of 16 children at the Childen's Medical Center, Boston. Seven of the children had leukemia, 7 had rheumatoid arthritis, 1 had nephrosis, and 1 had a Wilm's tumor. Seven of the children with malignant disease died too soon after transfusion for hepatitis to develop. One child with leukemia died 3 months after transfusion and was developing icterus at the time of death. Since he was known to have a terminal sepsis, it was felt that his jaundice might be due to bacterial infection.

Of the surviving 8 children, 4 have shown no signs of hepatitis and 4 have developed the disease.

Case Reports. CASE I. No. 373990. M.K., a 3-year-old white female, was first seen at the Children's Medical Center in June, 1951, because of rheumatoid arthritis. On Aug. 7, 1951, she received 200 cc. of postpartum plasma daily for 5 days. Although she felt somewhat improved symptomatically, her joint symptoms persisted. On Aug. 13, and for 3 successive days, she was given 50 cc. of regular plasma, and on Aug. 21, was given 300 cc. of whole blood. Because of her failure to improve, she was given 200 cc. of postpartum plasma intravenously daily for 4 days starting on Aug. 22. This again produced no improvement. On Aug. 20, cortisone was begun and two small transfusions of human albumin were administered on Sept. 2 and Sept. 4.

Her general condition remained unchanged until Dec. 17 when she was noted to have scleral icterus. Liver function tests were as follows: Thymol turbidity 14.0, thymol flocculation 3 to 4+, cephalin-cholesterol flocculation 4+, one-minute bilirubin 4.4 mg. and total serum bilirubin 8.7 mg. On Jan. 4, 1952, she was readmitted to the hospital because of marked icterus of the sclerae and skin. She was also noted to have loose stools and dark urine. Physical examination showed the liver to be 11 cm. below the right costal margin and diffusely tender. Her urine revealed 4+ bile, and urobilinogen was present in 1:4 dilution. The total protein was 7.48 gm. At that time, her thymol turbidity was 4.0, thymol flocculation 2 to 3+, cephalin-cholesterol flocculation 3 to 4+, one-minute bilirubin 7.9 mg., and total serum bilirubin 15.0 mg. There was no improvement of her joint symptoms during this period of intense jaundice.

She was treated with bed rest, a high-protein, high vitamin diet, and observed closely. Her liver function tests remained unchanged until Feb. 7, when they began to return to normal. By March, 1952, she was

free of jaundice and felt much improved although her joint symptoms remained unchanged. Liver function tests on July 7, 1952 were entirely normal.

CASE 2. No. 374306. R.M., a 9-year-old white male, was first seen at the Children's Medical Center in June, 1951, because of rheumatoid arthritis. On Aug. 29, he was given 200 cc. of postpartum plasma intravenously. Following this, the patient had a severe febrile reaction. His temperature rose to 105° F. and was controlled with aspirin. On Sept. 8, using a different lot of material, he was given a total of 4 transfusions of 200 cc. of postpartum plasma intravenously on successive days. He showed no improvement following this treatment. He received no regular plasma or whole blood prior to or subsequent to this therapy.

He was followed closely, and routine liver function tests performed on Oct. 24, 1951, were found to be within normal limits. On Nov. 4, the patient developed symptoms of anorexia, nausea, and vomiting, and shortly afterwards became markedly jaundiced and started passing dark urine and clay colored stools. The liver was found to be 5 cm. below the right costal margin and tender. The urine contained 4+ bile, and urobilinogen was present in dilutions of 1:256. The thymol turbidity was 22.0, thymol flocculation 3 to 4+, cephalin-cholesterol flocculation 3+, one-minute bilirubin 2.06 mg., and total serum bilirubin 3.2 mg. The bromsulfalein excretion test showed 41% retention at the end of 60 minutes using a 5 mg./kg. test dose. Serum albumin was 2.84 gm. and serum globulin 2.44 gm. There was no evidence of joint improvement during the period of maximum jaundice.

The patient was treated with bed rest, high-protein diet, and added vitamins. His liver function tests remained positive until Jan. 5, 1952, when they returned to normal. He has been followed for 6 months since recovery and has been well except for his arthritic symptoms which have remained unchanged. His liver function tests have continued to be normal.

CASE 3. No. 369732. M.D., an 8½-year-old white female with nephrosis, had been treated at the Children's Medical Center with antibiotics, salt-free albumin, and ACTH with little improvement. On April 6, 1951, she was given 200 cc. of postpartum plasma intravenously and this was continued for 3 successive days in an attempt to induce diuresis. This was unsuccessful, she gained 5 pounds, and required paracentesis. She had received no blood or plasma prior to this time, but on April 24, she was given 300 cc. of whole blood intravenously because of a fall in hemoglobin.

She was given cortisone, developed a diuresis, and was symptom-free until she was admitted to the hospital on May 30, 1951, with jaundice of one day's duration. There was a yellow tinge to her skin and her sclerae were quite icteric. The liver was 3 cm. below the right costal margin. Her urine contained bile. Thymol turbidity was 15.0, thymol flocculation 3+, cephalin-cholesterol flocculation 3 to 4+, one-minute bilirubin 3.41 mg., and total serum bilirubin 4.97 mg.

She was placed on a high-protein, low-fat diet, and on complete bed rest. Her jaundice cleared and she made a rapid recovery. When next seen on July 3, 1951, she appeared to be completely well. Repeat liver function tests were within normal limits.

CASE 4. No. 221159. J.H., a 16-year-old white male, had been followed at the Children's Medical Center for several years for rheumatoid arthritis. At no time had he received blood or plasma. On Sept. 20, 1951, he was started on a course of 200 cc. of postpartum plasma intravenously daily for 5 successive days. He showed no improvement as a result of this therapy and was discharged home.

On Nov. 11, 1951, he was noted by his physician to have icteric skin and sclerae and a diffusely enlarged and tender liver. His urine at this time was very dark. No laboratory tests were done. He was treated with bed rest, high protein diet and improved steadily. When seen again on Mar. 19, 1952, he was completely well except for his arthritis, which had not improved despite his jaundice. Liver function tests showed thymol turbidity 0, thymol flocculation 0, cephalin-cholesterol flocculation 0, one-minute bilirubin 0.51 mg., and total serum bilirubin 1.17 mg.

It is unfortunate that the laboratory data on Case 4 are incomplete. However, the clinical picture and physical findings were in keeping with a diagnosis of homologous serum hepatitis. In Case 1, whole blood and regular plasma were given at the same time as postpartum plasma, making the etiology of the hepatitis uncertain. On the other hand, the transfusion of whole blood in Case 3 was probably given too soon before the onset of symptoms to have been responsible for hepatitis. The infusion of human albumin in

Cases 1 and 3 were probably not responsible for the hepatitis, on the basis of the survey by Paine and Janeway[20].

The material administered to these 4 patients came from 5 different lots, and no 2 patients received material from the same lot. The high incidence of serum hepatitis found in this small group would indicate that homologous serum hepatitis can be transmitted through Fraction IV, and certainly confirms the fact that the danger of hepatitis is markedly increased when plasma is pooled. Whether or not the risk is increased by employing postpartum plasma instead of regular plasma, or by employing Fraction IV in contrast to non-fractionated pooled plasma, remains to be determined, although the studies of Granirer[5,6] and Aronson[1] would suggest that non-fractionated pooled postpartum plasma carries little risk.

The present series is too small to evaluate properly the usefulness of postpartum plasma in any of the conditions treated. Except for Case 1, which showed some subjective improvement, there was no evidence of a sustained remission in any of the patients with rheumatoid arthritis. It would appear from this study that the risk of acquiring hepatitis far outweighs the therapeutic effect of the material. An interesting finding was that none of the children with rheumatoid arthritis showed symptomatic improvement during the acute phase of hepatitis, as reported by Hench[8-12] and Holbrook[13].

Summary. 1. Four out of 16 patients treated with Cohn's Fraction IV of pooled postpartum plasma developed homologous serum hepatitis.

2. Therapy consisting of any type of plasma pool carries with it the risk of homologous serum hepatitis; the greater the number of donors contributing to a pool, the greater the risk.

3. In the small series studied, the risk of homologous serum hepatitis from Fraction IV of pooled plasma seems particularly great.

4. No beneficial effect on rheumatoid arthritis can be attributed to Fraction IV.

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EFFECT OF ORAL ADMINISTRATION OF COMBINATIONS OF PENTYLENETETRAZOL AND BARBITURATES*

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Despite the voluminous literature on barbiturates and on central analeptics[3,4,5,8,13], little attention has been given to the effects of the oral administration of these agents, which is the more regrettable since the vast majority of barbiturates are taken by this route. This study deals with the stimulating, hypnotic, anesthetic and lethal effects of the oral administration of pentylenetetrazol, of barbiturates, and of their combinations. This investigation will reveal whether the well-known physiological antagonism between pentylenetetrazol and barbiturates also occurs following their simultaneous oral administration. Furthermore, it will be determined if a fixed proportion of a combination of pentylenetetrazol and barbiturates given orally will interfere with the sedative or hypnotic action of barbiturates and if similar combinations in larger amounts will protect against an anesthetic or toxic dose of barbiturates.

Methods. Animal Experiments. Various doses of several barbiturates (long- and short-acting) and of pentylenetetrazol, as well as mixtures of these drugs, were administered by stomach tube to fasting dogs. Efforts (usually successful) were made to prevent vomiting following the administration of pentylenetetrazol and of pentylenetetrazol-barbiturate mixtures. Occasionally these drugs were administered in tablet form so that the insertion of the stomach tube was unnecessary. Signs indicating either stimulation or depression of the central nervous system were recorded. Since the barbiturates were administered either in anesthetic or lethal doses, and also in combinations with pentylenetetrazol, particular attention was paid to the onset, depth and duration of anesthetic action in control animals as compared with those receiving the combinations.

Clinical Investigations. In human studies, the barbiturates were administered alone or simultaneously with pentylenetetrazol, either in solution, in tablets or capsules. Various amounts of pentylenetetrazol were given in tablets with starch and talc as excipients. In a second series of experiments, products were prepared (with identical excipients) which contained a fixed amount of barbiturates and of pentylenetetrazol in a proportion of 1.5 parts of pentylenetetrazol to 1 part of barbiturate. In a third series, the proportion of pentylenetetrazol to pentobarbital or secobarbital was increased to a ratio of 3:1. Control experiments were also carried out, using barbiturates or pentylenetetrazol alone, and the sleep pattern following ingestion of various amounts of these agents was determined. The subjects received the medication approximately 3 hours after eating. Following their ingestion, the room was darkened and the patients' condition periodically ascertained as to onset, depth and duration of sleep. Patients receiving larger doses of the combination (pentylenetetrazol and barbiturates) were initially given the drugs in solution, but later tablets containing pentylenetetrazol and barbiturates in the above-mentioned ratios were substituted.

* We are grateful to Dr. James C. Munch, Medical Director, Strong Cobb & Co., Inc., Cleveland, Ohio, for making these Tetrobarb-combinations available to us for study.

Results. 1. ANIMAL EXPERIMENTS. *A. Effects of Orally-Administered Pentylenetetrazol:* Pentylenetetrazol was administered in doses of 35, 50, 75 and 200 mg./kg. of body weight (Table 1). After 35 mg./kg. of pentylenetetrazol, there was no excitement, but a gait resembling the steppage type was noted. Dogs receiving larger amounts of pentylenetetrazol showed signs of medullary stimulation, as evidenced by hyperpnea, nausea, retching, salivation, micturition and frequent defecation. Twitches or convulsions were seen only once in dogs receiving 50 mg./kg. of pentylenetetrazol. Hyperexcitability and spasticity persisted from 4 to 6 hours. Animals receiving 75 mg./kg. showed the same signs for a somewhat longer period, and an increased frequency of convulsions. All animals receiving 100 mg. of pentylenetetrazol per kg. had repeated tonic and clonic convulsions and were in a constant state of hyperexcitability for more than 6 hours. The onset of central nervous system stimulation in all cases was prompt, some animals convulsing within 5 minutes following oral administration of pentylenetetrazol. Animals showing frank convulsive seizures exhibited somnolence and anorexia following the period of hyperexcitability. In no instance did the animals die following the oral administration of 100 mg./kg. of pentylenetetrazol. But 200 mg./kg. of pentylenetetrazol proved fatal within one hour after its administration. These dogs showed tonic and clonic spasms, each lasting about 50 seconds at about 3-minute intervals. After 40 minutes the spasms became weaker, the animals seemed more relaxed, respiration ceased suddenly, the heart beating for a minute or two following respiratory failure.

TABLE 1.—EFFECTS OF ORAL ADMINISTRATION OF PENTYLENETETRAZOL ON DOGS

No. Animals	*Dose mg./kg.*	*Onset of Action (Minutes)*	*Magnitude of Response* ****	*Duration of Action (Hours)**
1	50	4	One abortive clonic spasm	3
3	50	3	Hyperexcitability	3
2	75	4	Convulsions	4
2	75	7	Hyperexcitability	4
8**	100	4–12	Tonic and clonic convulsions	5–6
3***	150	4–12	Tonic and clonic convulsions	8
3	200	2	Tonic and clonic convulsions	All died within 1 hour

* Hyperexcitability and spasticity.
** Four animals received drug in tablet form.
*** All animals received drug in tablet form.
**** Retching, salivation, defecation, micturition developed in all animals following the administration of pentylenetetrazol.

B. Effects of Orally-Administered Pentylenetetrazol-Pentobarbital Sodium Combinations. Pentylenetetrazol and pentobarbital sodium were simultaneously administered in the following combinations: (1) Pentobarbital sodium, 35 mg./kg. and pentylenetetrazol, 35 mg./kg. (2) Pentobarbital sodium, 35 mg./kg. and pentylenetetrazol, 100 mg./kg. (3) Pentobarbital sodium, 75 mg./kg. and pentylenetetrazol, 200 mg./kg. (4) Pentobarbital sodium, 100 mg./kg. and pentylenetet-

razol, 300 mg./kg. Tables 2 and 3 present the results obtained in animals given pentobarbital sodium alone and in the above-mentioned combinations.

Pentobarbital sodium alone, 35 mg./kg., produced surgical anesthesia within less than 15 minutes after its administration, lasting for several hours. When given in combination with pentylenetetrazol, 35 mg./kg., anesthetic action of the barbiturate remained uninfluenced. When given in combination with pentylenetetrazol, 100 mg./kg., the majority of the animals not only did not become anesthetized but did not go to sleep at all and showed only varying degrees of ataxia. It may be added that these animals also showed nausea, retching, urination, and defecation but no hyperexcitability no hyperpnea and no convulsions.

The animals receiving pentobarbital sodium, 75 mg./kg., and pentylenetetrazol, 200 mg./kg., showed a marked delay of onset of anesthetic action, but finally did become anesthetized. There was no hyperexcitability; one animal recovered and one died.

Animals receiving pentobarbital sodium, 100 mg./kg., and pentylenetetrazol, 300 mg./kg., (Table 3) likewise showed a delay of onset of anesthetic action; all animals became anesthetized. The control animals died within 2.5 hours; 2 animals receiving the pentylenetetrazol and pentobarbital sodium survived; the other 4 died within 24 hours. Of 4 dogs receiving pentobarbital sodium, 35 mg./kg., and pentylenetetrazol, 300 mg./kg., 3 showed one slight clonic spasm lasting for a few seconds within a few minutes after administration. The fourth animal did not show any evidence of seizure. These animals later became severely ataxic, did not become anesthetized, but their locomotion and postural re-

TABLE 2.—EFFECTS OF ORAL ADMINISTRATION OF PENTYLENETETRAZOL, PENTOBARBITAL SODIUM, AND THEIR COMBINATION IN A 1:1 RATIO ON DOGS

			Dose Administered Mg./kg.		
Dog No.	*Wt. kg.*	*Time of Adm. A.M.*	*PTZ**	*Phenobarb. Sodium*	*Results*
1	7.4	10:20	0	35	10:23 Ataxia 10:25 Prostrate 10:32 Surgical anesthesia Recovered after 5 hrs.
2	5.9	10:31	35	0	10:42 Little stiffness 10:50 Definitely stiff, urination and defecation 3:15 p.m. Completely recovered
3	9.3	10:53	35	35	10:56 Severe ataxia 11:02 Surgical anesthesia Recovered after 4 hrs.
4	5.0	10:36	35	35	10:38 Ataxia 10:53 Cannot stand 11:02 Prostrate 11:50 Surgical anesthesia Recovered after 5 hrs.
5	6.7	10:16	35	35	10:20 Ataxia 10:24 Cannot stand 10:35 Surgical anesthesia Recovered after 5 hrs.

* Pentylenetetrazol, USP

The fourth animal did not show any evidence of seizure. These animals later became severely ataxic, did not become anesthetized, but their locomotion and postural re-

flexes were more disturbed than those receiving pentylenetetrazol, 100 mg./kg. These animals recovered and one died from a previously existing respiratory infection.

C. Effects of Orally-Administered Pentylenetetrazol and Phenobarbital Sodium Combinations. Control animals were given phenobarbital sodium, 150 and 200 mg./kg., orally in solution (Table 4). Within 30 minutes they became prostrate and after 60 minutes they were anesthetized. They all died within 10 hours following administration. The animals given phenobarbital sodium, 200 mg./kg., and pentylenetetrazol, 300 mg./kg., simultaneously, in contrast to the animals receiving pentylenetetrazol-pentobarbital sodium mixtures, all showed from 1 to 7 clonic seizures within 10 minutes following administration. The animals did not become anesthetized until about 8 hours following administration; they survived at least 10 hours longer than control animals. Two animals recovered. Following the seizures at the time when the phenobarbital should begin to exert its central nervous system depressant effect, the animals, instead of becoming comatose, usually got up and walked about.

TABLE 3.—EFFECTS OF ORAL ADMINISTRATION OF PENTYLENETETRAZOL, PENTOBARBITAL SODIUM, AND THEIR COMBINATION ON DOGS

	Dose Administered mg./kg.					
No. Dogs	*PTZ**	*Pentobarb. Sodium*	*Onset of Maximum Action (Minutes)*	*Response*	*Duration of Action (Hours)*	*Remarks*
24	0	35	5–15	Surgical anesthesia	3–5	
13	100	35	5 (1 dog)	Surgical anesthesia	4	Defecation, occasional retching, no convulsion or sleep
			35 (6 dogs)	Severe ataxia, reflexes and body righting	4–5	
			30 (6 dogs)	Slight ataxia, able to stand and walk	3–4	
4	300	35	3 (3 dogs)	Spasm, severe ataxia	4–5	No anesthesia until recovery in 3 dogs; 1, no anesthesia for 5 hrs., found dead next day
2	0	75	3 5	Surgical anesthesia		Died in less than 24 hrs.
2	200	75	Over 60	Surgical anesthesia; no spasms		1 died; 1 recovered next day
3	0	100	3	Surgical anesthesia		Died 1–3 hrs.
6	300	100	30; 35; 40; 45; 50; 60	Surgical anesthesia; no spasms		4 died 6–18 hrs.; 2 recovered in 28 hrs. 1 recovered dog lapsed into coma several hrs. after recovery but normal 12 hrs. later

* Pentylenetetrazol, USP

2. HUMAN PHARMACOLOGICAL STUDIES. *A. Effects of Pentylenetetrazol.* Un-

selected subjects were given 300, 500, 600, 1200, 1800 and 3000 mg. or more of pentylenetetrazol (up to 45 mg./kg. of body weight) on an empty stomach (Table 5). While smaller doses (500 mg. or less total dose) do not seem to interfere with sleep pattern, progressively larger doses produce various objective and subjective signs and symptoms of central nervous system stimulation. These include nervousness, excitement, olfactory hallucinations,

TABLE 4.—EFFECTS OF ORAL ADMINISTRATION OF PENTYLENETETRAZOL, PHENOBARBITAL SODIUM, AND THEIR COMBINATION ON DOGS

	Dose Administered mg./kg.		*Onset of Action (Minutes)*		
No. Dogs	*PTZ**	*Phenobarb. Sodium*	*Prostration*	*Anesthesia*	*Remarks*
2	0	150	30	60	Both dogs died next day
4	0	200	17–30	50–60	All dogs died 6–20 hrs.
12	300	200	120–600	300–800	10 dogs died 24–32 hrs. 2 dogs recovered in about 60 hrs. All dogs showed clonic and tonic spasms within 11 minutes; 2 showed only 1 brief spasm, the others, 4–7. Following seizures, all dogs temporarily recovered without showing secondary depression

* Pentylenetetrazol, USP

TABLE 5.—THE EFFECTS OF ADMINISTRATION OF PENTYLENETETRAZOL ON HUMAN SUBJECTS

		Sleep Pattern			
No. Subjects	*Total Dose mg.*	*No Change*	*Disturbed*	*Improved*	*Remarks*
47	300	30	11	6	Subjects from medical, urological, orthopedic, surgical and psychiatric wards
10	500				3: olfactory hallucinations 2: jittery 2: slight gastrointestinal discomfort
5	500				Epileptics, no seizures
5	600				No discomfort
3	600	3			1: vertigo, nervous tension, unsteadiness
1	800				Excitement terminated with Amytal Na 200 mg. IV
1	1000	1			Usual sleep pattern
3	1000				Epileptics: 1 showed convulsions
2	1200	1	1		1 subject showed clonic jerks and given Amytal Na 500 mg. IV
2	1800	1	1		1 subject jittery; delay of onset of sleep
6	3000 to 3600	0	6		Subjects showed vomiting or retching; 3 convulsed. All given Amytal Na 500 mg. IV

light-headedness, nausea, retching, vomiting, and tonic and clonic convulsions.

B. Effects of Pentylenetetrazol-Barbiturate Combinations. Unselected subjects from the psychiatric, orthopedic, medical and urological services were given 200 mg. (total dose) of either secobarbital sodium, pentobarbital sodium, or phenobarbital sodium alone (Table 6) and in combinations with 300 or 600 mg. of pentylenetetrazol (total dose) (Table 7). It should be noted that their sleep was in no way disturbed or altered by the addition of pentylenetetrazol to the barbiturates in the above ratios. It is, therefore, evident that when barbiturates are used in hypnotic doses, the addition of pentylenetetrazol in the above-mentioned proportions did not interfere with the soporific effect of commonly used barbiturates.

A limited number of subjects were given 500 mg. pentobarbital sodium as controls, other subjects received 600 or 1000 mg. pentobarbital sodium in combination with 900, 1500, 1800 mg. pentylenetetrazol. The subjects receiving 500 mg. pentobarbital sodium alone did not differ significantly in their sleeping pattern from those receiving 1000 mg. pentobarbital sodium plus 1500 mg. pentylenetetrazol (Tables 6 and 7). Neither group of patients was anesthetized; they could be aroused easily; in fact, patients from each group awoke spontaneously to void (Table 7). Some subjects who received pentobarbital sodium, 15 mg./kg., combined with pentylenetetrazol, 45 mg./kg., showed delay of onset of sleep, restlessness, retching and vomiting within 3 hours following administration. They did not, however, show twitches or convulsions. Once they were asleep, they could be aroused easily and occasionally awoke spontaneously; some with, and others without ataxia. The duration of sleep varied. Some awoke spontaneously at their usual hour, feeling refreshed. Others were awake but were nevertheless somnolent, complaining of a feeling similar to that experienced after an alcoholic debauch. Control studies using pentobarbital sodium alone, 15 mg./kg., were not carried out because data in the literature indicate that doses of this magnitude may produce anesthesia with complications[4,5].

TABLE 6.—THE EFFECTS OF THE ADMINISTRATION OF BARBITURATES ON HUMAN SUBJECTS

Drug Sodium Salt	*Total Dose mg.*	*No. of Subjects*	*Sleep Pattern*			*Remarks*
			No Effect	*Disturbed*	*Improved*	
Phenobarbital	200	16	4	5	7	2 subjects confusion, disorientation upon awaking
Pentobarbital	200	47	5	9		2 confused, disoriented
	500	3			3	All could be aroused but ataxic and dizzy on awakening
	600	3			3	
Secobarbital	200	18	4	3	11	1 subject confused and noisy

Discussion. The concept that pentylenetetrazol is rapidly destroyed in the human organism originates from (a) clinical experience in which the drug is given intravenously every 15 minutes to patients in the treatment of acute barbiturate intoxication, (b) from animal experimentation of a similar nature, and (c) from a case of suicide who died one hour following the ingestion of 10 gm. of pentylenetetrazol and from whose tissues and urine only traces of pentylenetetrazol were recovered[2]. However, in unprotected animals given pentylenetetrazol subcutaneously or orally, its prolonged action has been reported[6,7]. Hildebrandt and Voss attempted to determine the rate of detoxication by giving half the convulsant dose subcutaneously or orally at varying time intervals. With an interval of 20 minutes between doses, two times a half-convulsant dose produced convulsions, but when the interval was increased to a half-hour and to one hour, three such doses were necessary. With an interval of 2 hours, detoxification was more rapid than absorption, so that no convulsions were produced. These findings are in agreement with those reported in this paper and show that pentylenetetrazol administered by the oral route is not eliminated much faster "essentially" than some barbiturates. Also, it should be remembered that the duration of action varies with the size of the dose. In our experiments, pentylenetetrazol,

TABLE 7.—THE EFFECTS OF THE ADMINISTRATION OF COMBINATIONS OF PENTYLENETETRAZOL AND BARBITURATES ON HUMAN SUBJECTS

Drug	*Dose*** (*mg. total*)	*No. of Subjects*	*Sleep Pattern*			*Remarks*
			No Change	*Disturbed*	*Improved*	
PTZ*	300	16	3	2	11	
Phenobarb. sodium	200					
PTZ	300	51	7	4	40	
Pentobarb. sodium	200					
	600	14	1	0	13	3 subjects dizzy on awakening
	200					
	1500	3	0	0	3	Subjects could be aroused easily
	1000					
	1800	3	0	0	3	Subjects could be aroused easily; no ataxia
	600					
	3200–3600	6	0	6	0	3 subjects showed retching and vomiting. 5 delay in onset of sleep, no convulsion. 5 aroused easily. Only 1 did not awaken spontaneously on the following morning
	1000–1200					
PTZ	300	20	5	2	13	
Secobarb. sodium	200					

* Pentylenetetrazol, USP

** In this column, the first number refers to mg. of PTZ; the second number refers to mg. of the barbiturate

when given in doses of 50 to 150 mg./kg. orally to dogs, powerfully stimulated the central nervous system for periods up to 8 hours.

It should be emphasized that pentylenetetrazol is a general central nervous system stimulant[1], producing not only vomiting but also hyperpnea, micturition and defecation. This is in agreement with the seldom-quoted experiment by Schwartz[12]; namely, that 40 and 80 mg./kg. overcame the paralysis of the vomiting center which occurred in deep barbital anesthesia. In addition, it should be pointed out that in the previous literature[6], the oral convulsive dose for pentylenetetrazol in rabbits was reported as between 140 and 200 mg./kg.; in rats, from 170 to 180 mg./kg. Our results show that considerably less pentylenetetrazol produced convulsions in dogs, and still less is required for humans.

In spite of the well-known central stimulating effect of pentylenetetrazol, we have shown in normal subjects that a total oral dose as high as 300 to 500 mg. may not stimulate the subject nor interfere in any way with his normal sleep pattern. In fact, some of the subjects who received this dose fell asleep while their electroencephalographic tracings were being recorded. Even when 3000 mg. (pentylenetetrazol, 35 mg./kg.) was given orally to 4 subjects, one was not affected, one complained of nervousness, but went to sleep without any difficulty. The other two developed nausea and persistent vomiting which were terminated abruptly by the intravenous injection of sodium amytal. In all 4 cases no other evidence of central nervous system stimulation was observed (Table 5).

The administration of suitable single oral doses of pentylenetetrazol with full oral anesthetic doses of barbiturates prevents or delays narcosis: a finding which agrees with the results of numerous previous investigations, in which, however, the drugs were administered by the intravenous route. Cats received preliminary anesthesia for surgery[9] and were given intravenously a solution of either pernoston or evipal sodium, alone in doses of 100 mg./kg./hr., or in combination with doses of pentylenetetrazol (from 50 up to 250 mg./kg.). The fatal dose of pernoston alone was 90 mg./kg./hr., whereas that of evipal sodium alone was 150 mg./kg./hr. The addition of pentylenetetrazol, 100 and of 250 mg./kg./hr., to pernoston raised the fatal dose of the latter from 90 to 117 and to 148 mg./kg./hr. The addition of pentylenetetrazol, 50 mg./kg./hr., raised the fatal dose of evipal from 150 to 350 mg./kg./hr., and the addition of pentylenetetrazol, 150 mg./kg./hr., raised the fatal dose of this barbiturate to 487 mg./kg./hr.[14].

In our experience, the combined oral administration of pentylenetetrazol and barbiturates delayed considerably the onset of action of massive oral doses of barbiturates and prolonged life. In the case of pentobarbital sodium, the above-mentioned combination in some cases prevented narcosis altogether and in others it prolonged the onset of action of the barbiturate and shortened its duration of action. Although pentylenetetrazol, 200 mg./kg., is fatal to dogs within 1 hour, the combined oral administration of pentobarbital sodium, 35 mg./kg., and pentylenetetrazol, 300 mg./kg., is not fatal, the animals exhibiting only one brief clonic spasm or no seizures at all. With regard to combinations of pentylenetetrazol with the longest acting barbiturate, phenobarbital sodium, several points should be discussed. It should be recalled that the combined administration of pentylenetetrazol and pentobarbital sodium in a proportion of 3:1 did not result in hyperexcitability, much less in clonic and tonic

seizures. The combined administration of phenobarbital sodium and pentylenetetrazol in the proportion of 3:2 always resulted in hyperexcitability and convulsions, sometimes as many as 7 convulsive seizures supervening within 20 minutes following oral administration. This shows that pentylenetetrazol reaches the effector cells sooner than phenobarbital, which is not the case with pentobarbital. Nevertheless, pentylenetetrazol protects animals against phenobarbital just as significantly as it does against pentobarbital sodium. Pentylenetetrazol, in combination with phenobarbital, delays the onset of prostration and anesthesia; prolongs, and in some cases, saves lives.

These observations, plus the observations of Koppanyi, Linegar and Dille[10] that simultaneous intravenous injection of 1 to 3 mg. of coriamyrtin/kg., and from 20 to 40 mg./kg. of pentobarbital sodium was not followed by sleep or anesthesia of the animals but only by ataxia, do not support the claims of Nilsson[11], who rejects the use of analeptics in the treatment of acute barbiturate poisoning.

These observations indicate that pentylenetetrazol is most effective in antagonizing anesthetic or toxic effects of barbiturates when given in definite amounts with barbiturates. This ratio varies with the individual barbiturate.

Subjects given hypnotic doses of short- and long-acting barbiturates in combination with pentylenetetrazol in a ratio of 1:3 and 1:1.5 respectively, slept as well as control patients given the same dose of barbiturate alone. This shows that therapeutic combinations of pentylenetetrazol and barbiturates do not interfere with the hypnotic effects. This should not be surprising in view of the fact that oral doses of pentylenetetrazol alone as high as 600 mg. did not interfere with the sleep cycle of subjects.

Preliminary observations indicate that when pentylenetetrazol is given in conjunction with large doses of pentobarbital sodium (500 to 1000 mg.), antagonism in humans similar to that noted in the animal experiments is evident.

Summary. 1. The effect of oral administration of various doses of pentylenetetrazol was determined.

2. The duration of action of orally-administered pentylenetetrazol extends over hours both in dogs and in humans. The oral convulsant dose for dogs lies between 75 and 100 mg./kg., whereas for humans it is more than 35 mg./kg.

3. The combination of pentylenetetrazol and pentobarbital or secobarbital sodium in the ratio of 3:1, and pentylenetetrazol and phenobarbital sodium in the ratio of approximately 3:2, in anesthetic or fatal doses of the barbiturates, delayed or prevented the onset of anesthesia; prolonged, and often saved the lives of the experimental animals.

4. Relatively small doses of barbiturates protect animals against fatal doses of pentylenetetrazol. Pentobarbital sodium, 35 mg./kg., prevents convulsions from pentylenetetrazol when given in doses of 100 mg./kg., and occasionally even when given in doses of 300 mg./kg. When phenobarbital and pentylenetetrazol are administered simultaneously there are a few convulsive seizures before the anticonvulsant effect of phenobarbital becomes manifest.

5. Subjects given therapeutic doses of pentylenetetrazol and barbiturates in ratios of 3:1 for pentylenetetrazol-pentobarbital sodium, or pentylenetetrazol-secobarbital sodium, and of 3:2 for pentylenetetrazol-phenobarbital sodium showed the same sleep pattern as subjects given the same doses of barbiturates alone.

6. Subjects given pentylenetetrazol and large doses of pentobarbital sodium

in proportion of 3:1 could be easily aroused.

7. The significance of these findings is discussed.

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THE EFFECT OF INTRAVENOUS AND INTRAMUSCULAR PARITOL ON THE CLOTTING TIME

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Paritol* is a synthetic anticoagulant which retards the clotting time of blood by inhibiting the action of thrombin. It is the sodium salt of polyanhydromannuronic acid sulfuric ester produced by treating kelp seaweed extract with sulfuric acid[6]. Its chemical structure and action are thought to resemble closely that of heparin.

The effect of Paritol when administered intravenously or intramuscularly on the clotting time and on the prothrombin time has been studied at the animal and clinical levels. The value of protamine sulfate as an antidote has been ascertained.

Methods. 1) Paritol A† was administered intravenously to 22 dogs in doses of 4 to 7 mg./kg. body weight. Clotting times were determined by the Lee-White method[2]. Protamine sulfate and toluidine blue were given intravenously to 5 dogs after the clotting time had been prolonged by the administration of Paritol.

2) Paritol C** was administered intravenously to 23 patients in doses of 5 mg./kg. body weight initially. Subsequently it was given in doses of 3 to 5 mg./kg. body weight when the clotting time dropped below 20 minutes. Serial clotting times and prothrombin times were determined by the Link-Shapiro[3] modification of the Quick[4] method.

3) After a control clotting time, a single dose of Paritol M‡ was administered intramuscularly in doses of 7.5 mg./kg. to 15 patients. Clotting times were performed serially from 30 minutes to 24 hours to determine its total duration of effect.

4) To study the duration of repeated injections, Paritol M was administered at 12-hour intervals for 2 doses to 8 controls and the Lee-White clotting times and the prothrombin times were serially determined over a 24-hour period of time.

5) Protamine sulfate was given intravenously in doses of 50 mg. to 2 patients and 100 mg. to 4 patients at the time of maximal prolongation of clotting time following Paritol M administration.

6) Control and serial determinations of urine, blood urea nitrogen, prothrombin activity, and bromsulfalein excretion were made in 11 patients receiving Paritol M.

Results. Animal studies revealed that Paritol A in doses of 5 mg./kg. body weight administered intravenously was optimum in prolonging clotting time to therapeutic levels of 20 to 60 minutes (Fig. 1). A peak clotting time was reached in 15 to 30 minutes with prolongation to 20 to 60 minutes for

* Supplied through the generosity of Wyeth, Incorporated.

† Paritol A was used only in animals.

** Paritol C is a more purified product and is suitable for administration to human beings.

‡ Paritol M is Paritol C prepared for intramuscular administration.

4 to 5 hours. Protamine sulfate in doses of 3 mg./kg. body weight administered intravenously effects a prompt return of the clotting time to normal, but toluidine blue in doses of 3 mg./kg. body weight administered intravenously was not reliable (Fig. 2).

No clinical thromboses or emboli developed in 23 patients maintained on intravenous Paritol for 24 to 72 hours.

Effect of Various Doses of Paritol A on the Lee White Clotting Time in 22 Dogs

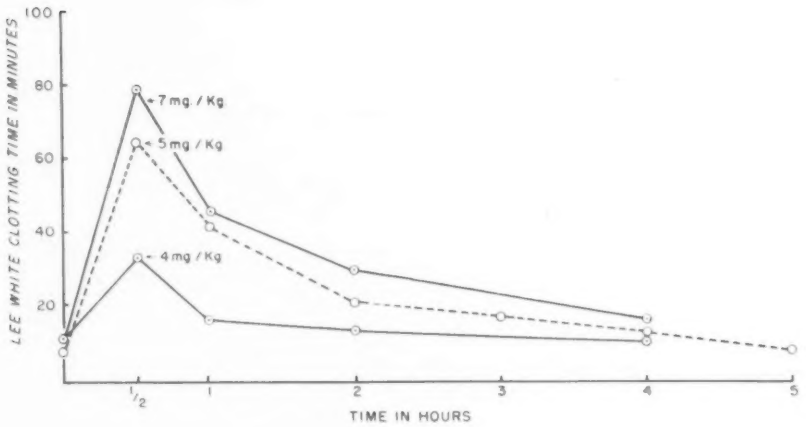

Fig. 1.

Five Dogs Treated with Paritol A Plus Protamine Sulfate

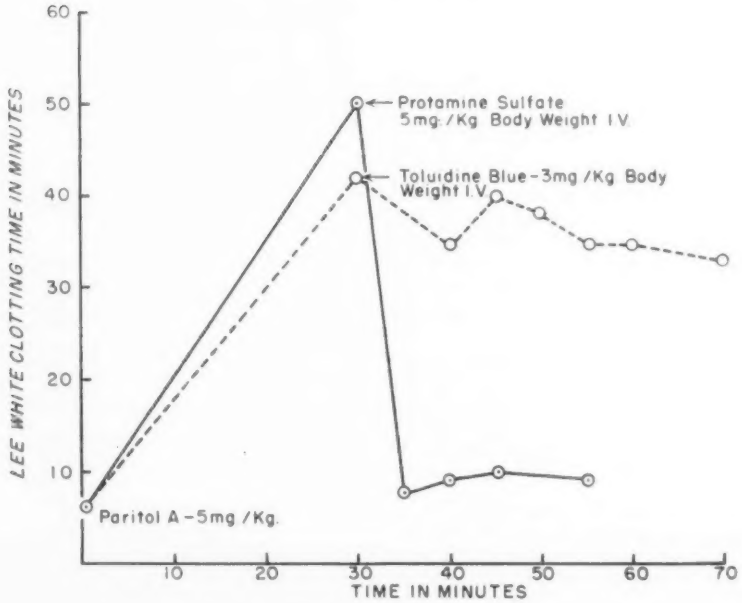

Fig. 2.

These included 7 controls, 3 with generalized arteriosclerosis, 9 with recent myocardial infarctions and 4 with thrombophlebitis. Toxic effects included transient numbness and tingling of fingers and toes. Slight transient hypotensive responses were occasionally seen, but shock was not encountered. Patients initially received a dose of 5 mg./kg. body weight of Paritol C intravenously and from 3 to 5 mg./kg. body weight intravenously when the clotting time fell below 20 minutes. In these the clotting time was effectively prolonged to 10 hours with extremes of 8 to 12 hours. Five patients required additional Paritol only at 12-hour intervals. Figure 3 represents a typical case treated with intravenous Paritol. Rapid excessive prolongation of the clotting time occurred initially with each intravenous administration. In 15 patients the prothrombin time was slightly prolonged. In 2 the prothrombin time dropped from 90% to 10% of normal within 24 hours without Dicumarol.

Paritol C Administered Intravenously until Therapeutic Level of Prothrombin Activity Reached with Dicoumarol

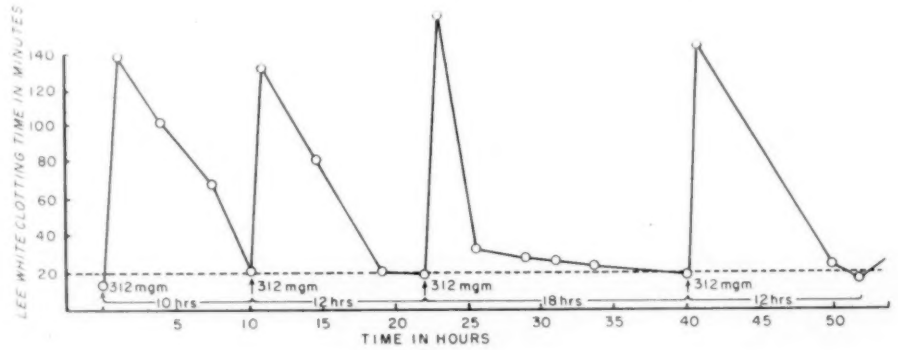

Fig. 3.

When Paritol M was administered intramuscularly in doses of 7.5 mg./kg. body weight, there was a more gradual prolongation of the clotting time, requiring about 1 hour for effective therapeutic levels to be reached. The excessive prolongation encountered with intravenous Paritol administration was not seen. Therapeutic levels following single injections were maintained on an average of 10 hours (Fig. 4). Intramuscular injections were repeated at 12-hour intervals and therapeutic levels were maintained for 24 hours. The clotting time was significantly more prolonged following the second injection of the same dose than it was following the initial dose, suggesting an accumulative effect (Fig. 5). Protamine sulfate was administered intravenously in doses of 50 mg. to 2 patients when the clotting time was prolonged with apparent effect. When the protamine sulfate was increased to 100 mg. in 4 subsequent patients, there was prompt return of the clotting time to approximate pretreatment levels. We believe the latter is an effective dose of the antidote.

Limited kidney and liver function studies were done on the patients receiving Paritol M to determine drug toxicity. Prothrombin activity was invariably prolonged but not to any significant extent, except in 2 cases where

Average Prolongation of Lee White Clotting Time in 16 Patients Receiving a Single Intramuscular Injection of Paritol M in Doses of 7.5 mg./Kg. Body Weight.

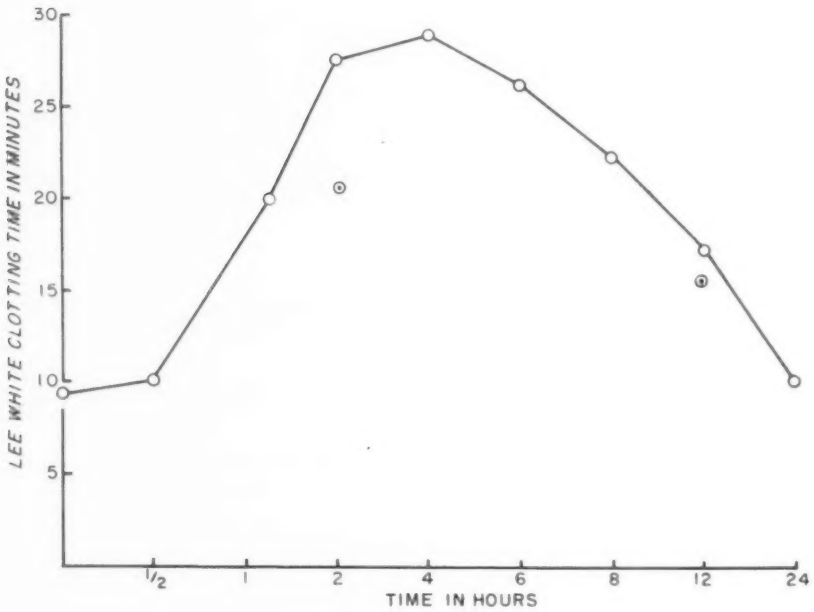

Fig. 4.

Cumulative Effect of Paritol M in 8 Patients Administered at 12 Hour Intervals in Doses of 7.5 mg./Kg Body Weight

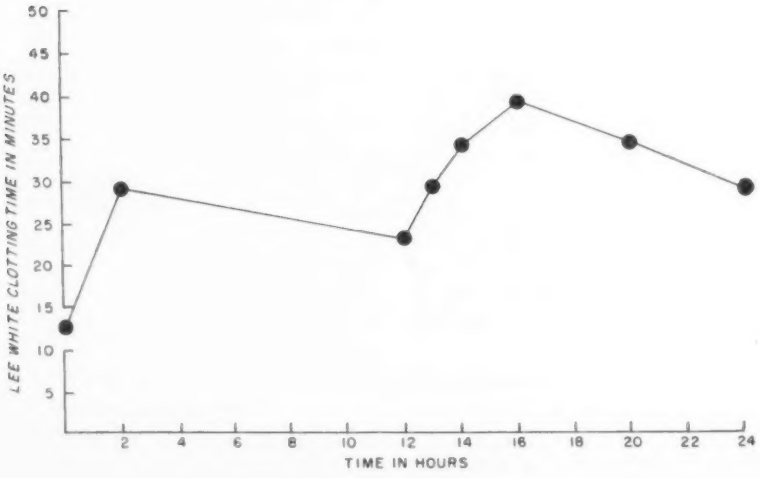

Fig. 5.

it dropped from 100 to 70% and from 75 to 50% respectively. There was little or no change in bromsulfalein excretion except in one patient, in whom retention increased from 16 to 28% in 30 minutes, 4 days after Paritol administration. After 7 days, retention had returned to 15%. There were no abnormalities found on routine urinalyses following therapy. Blood urea nitrogen was invariably increased from 1 to 27 mg. per 100 cc. with an average of 6 mg. per 100 cc. above the control level.

Only 2 patients of the 29 receiving intramuscular Paritol complained of excessive pain at the site of administration. All others stated that it was no worse than penicillin. There were no hematomas, sterile abscesses, or other local complications. There were systemic side effects in 2 patients. One complained of transient tingling of the fingers and toes and one complained of generalized aching and nausea which lasted about 24 hours. Shock-like effects were not seen with the intramuscular administrations.

Discussion. It is desirable for effective antithrombotic treatment that simultaneous administration of a rapidly acting anticoagulant be given with the oral coumarin agents to cover the period required for these substances to depress the blood prothrombin adequately. Heparin, because of its prompt prolongation of the clotting time, is widely used to cover this lag period which would otherwise leave the patient unprotected for a significant length of time. Because of the expense of heparin, a search has been made for a synthetic agent with similar properties. Paritol is a synthetic antithrombin which possesses some of these properties[6].

Following the use of Paritol in 35 patients, Sorenson and Wright, in comparing it to heparin, concluded that it produced a significant prolongation of the clotting time with duration of effect 2 to 3 times that of heparin and that mg. for mg. it was approximately one-seventh as potent as heparin[7]. Our observations made in 52 patients have shown that Paritol will effectively prolong the clotting time 8 to 10 hours whether given intravenously or intramuscularly. Intravenously administered Paritol caused a more rapid and an excessive prolongation of the clotting time. The response to intramuscularly administered Paritol was smoother and produced a more desirable curve (Fig. 6).

Systemic and sensitivity toxic reactions following intravenous Paritol have included hypotension, dizziness, nausea, and vomiting and tingling of extremities[1,7]. Localized inflammation may develop when accidental extravasation occurs[1,7]. Most reactions may be considered mild, but the anaphylactic and hypotensive reactions reported assumed rather alarming proportions and apparently occurred although careful attention was given to the rapidity of administration[1,7]. Alopecia has been reported when the total amount of Paritol used exceeded 2.8 gm.[5] and proves to be a very limiting factor in its usage.

There have been no major toxic reactions in our experiences with Paritol A, C, or M. Minor hypotensive responses have been encountered, but no shock-like episodes have occurred. In other series epinephrine and oxygen have been used effectively to treat the more severe hypotensive response[7]. There were 3 minor systemic reactions noted. In 2 patients reactions were manifested by transient tingling of fingers and toes and in another by generalized aching and nausea. The former lasted for only a few minutes and the latter persisted for about 24 hours. In an 8-month follow-up of our cases, no alopecia has been encountered, but we did not exceed a total

dosage of 1.68 gm. in any of the patients. In unselected cases, there was consistent urea retention following Paritol administration. This was minimal except in patients with advanced kidney disease.

Paritol intramuscularly in our experience would appear to be a safer mode of administration. Only 2 minor toxic manifestations occurred in 29 patients receiving 37 injections.

Admittedly Paritol M is not the true substitute for heparin, but it may be in the related field of substances when other similar compounds are tested. Because of cheapness of production, dependability in prolonging the clotting time for 8 to 10 hours intravenously or intramuscularly, and effectiveness of protamine sulfate as an antidote, it would appear that Paritol and other similar substances should be further evaluated. Limiting factors in the usage of Paritol appear to be its potential renal toxicity, its hypotensive effect, its anaphylactic propensities, and its tendency to produce total alopecia.

Summary. Paritol A, C, and M have been studied in animals and human beings. Single injections effectively prolonged the clotting time for 8 to 10 hours, and repeated doses every 8 to 10 hours adequately maintained satisfactory therapeutic levels. Paritol M caused minimal local reaction at the site of administration and appeared to be somewhat less toxic systemically than intravenously administered Paritol. Protamine sulfate was found to be an effective antidote against intravenously or intramuscularly administered Paritol. Paritol may produce a slight prolongation of the prothrombin time. It consistently caused a rise in the blood urea nitrogen and to a marked degree in patients with kidney disease. The usefulness of Paritol appears to be limited because of its toxic reactions.

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THE HYPERACTIVE CAROTID SINUS REFLEX OF THE CARDIO-INHIBITORY TYPE IN INDIVIDUALS WITH AURICULAR FIBRILLATION

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Some individuals with permanent auricular fibrillation develop attacks repeatedly of weakness, dizziness, faintness and syncope. In the absence of other ascertainable causes, these symptoms, and even sudden death, have been attributed to sudden increases in ventricular rate that cause an inadequate cardiac output of varying degree and duration. There is no doubt that rapid increases in ventricular rate in individuals with auricular fibrillation can produce these symptoms. It is commonplace to observe such symptoms following physical activity. The individual may, of course, be unaware of an increased ventricular rate, so that an historical relationship between the ventricular rate and the symptoms may be unobtainable. However, such symptoms do occur, at times, in individuals with auricular fibrillation without preceding physical exertion or apparent emotional disturbances. Unrecognized psychogenic disturbance, unrecognized tachycardia or a cerebral mechanism of nebulous nature is invoked frequently to explain the symptoms.

Recently, we have seen several individuals with auricular fibrillation who have had complaints that would have instantly suggested a carotid sinus syndrome had a normal sinus rhythm been present. So far as we are aware, a hyperactive carotid sinus reflex has not been reported in individuals with auricular fibrillation. Indeed, we are unfamiliar with any discussion of this possibility. It is, of course, recognized that the ventricular rate in individuals with auricular fibrillation can be slowed slightly by pressure upon the carotid sinus.

We know of no reason that the carotid sinus syndrome should not occur in individuals with auricular fibrillation. On the contrary, it would appear, on theoretical grounds, that the syndrome should be more common in those with auricular fibrillation than in those with a sinus rhythm. This is so because the carotid sinus tends to be more sensitive in those with cardiac disease, particularly coronary artery or hypertensive disease. Auricular fibrillation is frequently present in these abnormalities. Furthermore, digitalis is almost always used in individuals with auricular fibrillation. Digitalis increases the sensitivity of the carotid sinus.

The purpose of this report is to show that a hypersensitive carotid sinus of the cardio-inhibitory type does occur in some individuals with auricular fibrillation. Judged by this small series, the syndrome is at least as common in those with this arrhythmia as it is in those with a normal sinus rhythm.

Methods and Material. Twenty consecutive individuals with auricular fibrillation were studied. Seven gave a history of symptoms

that could have been produced possibly by a hyperactive carotid sinus reflex. Five of these 7 had a history of one or more episodes of syncope. There were 10 males and 10 females. The ages varied from 40 to 84 years. Two were in the fifth decade, 6 in the seventh, 8 in the eighth decade and 4 in the ninth decade of life. Two had chronic hypertension, one had coronary artery disease, 5 had both chronic hypertension and coronary artery disease, 4 had rheumatic heart disease and 2 of these had associated coronary artery disease, one had nutritional heart disease and 7 had enlarged hearts of undetermined etiology with associated peripheral arteriosclerotic vascular disease. All had enlarged hearts. All were receiving digitalis.

The carotid artery pulsations were located in the neck at the angle of the mandible. Pressure was applied by compressing and massaging the artery against the cervical vertebrae with the thumb anteriorly and the other fingers of the hand posteriorly. This allowed the observer direct vision of the patient and of the electrocardiogram. The patient was semi-recumbent with the head slightly extended and rotated to the opposite side. The right side was massaged first. Both sides were never massaged simultaneously. An electrocardiogram was obtained before, during and after massage of the carotid sinus. The lead employed was the one that demonstrated most clearly auricular complexes. As soon as electrocardiographic changes were obtained, pressure upon the carotid sinus was released, so as to avoid any untoward effects in this more susceptible group. All of these patients had advanced heart disease and we did not feel justified in risking irreversible cerebral changes that may occur[2,25]. For the same reason, pressure upon the carotid sinus was not applied with the patient standing.

Results. In 13 of the 20 individuals, carotid sinus pressure produced no significant decrease in ventricular rate or symptoms other than those attributable to direct local pressure. Two of these 13 had a history of syncope. In 7 (6 males and one female) of the 20, a hyperactive carotid sinus reflex of the cardio-inhibitory type was produced almost simultaneously. In 5 of these 7, symptoms previously experienced were reproduced. In 3, each with a history of syncope, ventricular standstill occurred. In the other 4, 2 of whom had a history of episodic dizziness and lightheadedness, the ventricular rate was abruptly slowed from 60 per minute, 70 per minute, 75 per minute, and 135 per minute to 28.8 per minute, 44 per minute, 37.7 per minute and 48 per minute respectively and became regular. In each of these, the configuration of the QRS complex changed. The QRS complex became larger in 2, an R wave was abolished in one, and, in another, the configuration of complete left bundle branch block of 9 years' duration was transformed to that of normal conduction.

In all but 3, pressure upon the right carotid sinus duplicated changes produced by pressure upon the left carotid sinus. In these 3 individuals, pressure upon the right carotid sinus produced no effect, whereas pressure upon the left carotid sinus produced ventricular standstill in one and ventricular slowing to a regular rhythm in 2.

The following case reports illustrate the hyperactive carotid sinus reflex of the cardio-inhibitory type in individuals with auricular fibrillation.

Case Reports. Case 1. L. M., a white female, 70 years old, was admitted to the Episcopal Hospital because of a painful shoulder of several hours' duration. She was performing her usual household chores when she suddenly "blacked-out" and fell down the stairs. When she reached the foot of the stairs, she was conscious and aware of pain in the left clavicular region. Because of increasing pain, discoloration and swelling of the left clavicular region, she was brought to the hospital. Examination revealed a tender, hemorrhagic area in the left mid-clavicular area. Roentgenographic study disclosed no fracture of the clavicle. There was evidence of old fractures in the region of the left humoral head and of the right ankle.

Inquiry revealed that she was in apparently good health until 2 years ago when fainting spells first appeared. Since then, fainting spells have recurred frequently. These transient episodes of unconsciousness may appear spontaneously or may be precipitated by stooping, lifting or carrying heavy loads. Occasionally, 3 or 4 attacks occur in rapid succession. She was not aware of either convulsions or incontinence. Attacks were preceded

frequently by transient blurred vision and lightheadedness. There was no residual weakness. She thinks that these spells represent heart attacks, for a doctor told her of heart disease 2 years ago. Since then, she has taken digitalis (0.1 gm. daily).

Examination of the heart revealed the point of maximal impulse to be in the sixth intercostal space at the left anterior axillary line. The rhythm was grossly irregular at a ventricular rate averaging 100 per minute. There was a pulse deficit of 10 per minute. The aortic second sound was slightly accentuated and was louder than the pulmonic second sound. There were no murmurs. The cervical veins were slightly distended. Basilar pulmonary rales were present. The liver was not palpable. There was no peripheral edema. The blood pressure was 160/80 mm. Hg. Funduscopic examination revealed a slight increase in light streak.

The electrocardiogram disclosed the presence of auricular fibrillation and an irregular ventricular rate averaging 110 per minute. There were ST-T alterations consistent with digitalis effect and myocardial disease.

Pressure upon the right carotid sinus resulted in an abrupt appearance of ventricular standstill (Fig. 1). Pressure was maintained only for purposes of electrocardiographic demonstration. When lightheadedness and pallor appeared, pressure was released. She stated that she experienced similar sensations spontaneously just before fainting. The electrocardiogram in Fig. 1 is a continuous tracing of lead V_1 and reveals the presence of auricular complexes, irregular in size and shape, at an average rate of 428 per minute and an irregular ventricular rate averaging 105 per minute. During carotid sinus massage, the auricular complexes are unchanged in size, shape or frequency and the ventricular complexes are absent. Pressure upon the left carotid sinus produced similar results.

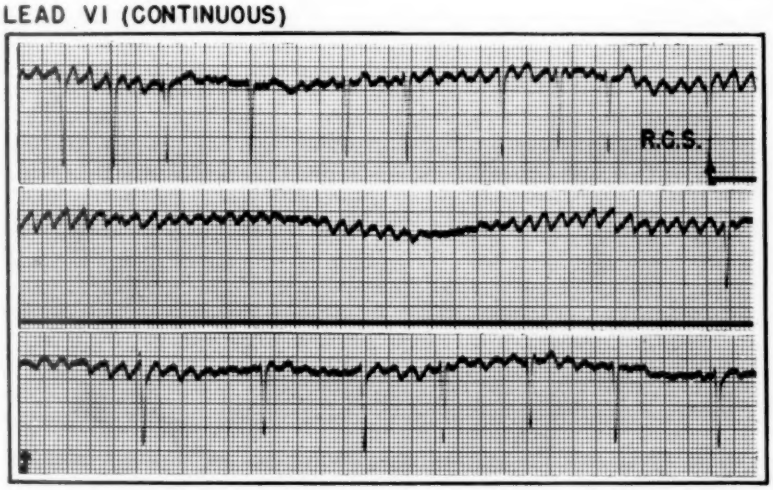

Fig. 1. Case 1. Continuous tracing, lead V_1. Initially, there is auricular fibrillation at an average ventricular rate of 105 per minute. Pressure upon the right carotid sinus (R.C.S.) results in ventricular standstill. The auricular complexes are not significantly changed. Pressure upon the left carotid sinus resulted in a similar effect.

Case 2. C. S., a 65-year old white male was admitted to the Episcopal Hospital because of pain in his right chest. The night before admission, while walking, he suddenly experienced dizziness and fell upon his right side. He did not lose consciousness. He got up and returned home. He noticed a painful sensation in the right side of his chest, especially upon coughing or deep breathing. When shortness of breath appeared, he came to the hospital for relief.

He stated that he has had "heart trouble" for 8 years. Eight years ago, he saw "spots" before his eyes, fell and injured his shoulder and right chest. Shortness of breath was also present. He was hospitalized at that time and told that he had a heart attack. Since that time, he has had 5 episodes of sudden faint-

ing. He takes digitalis (0.1 gm.) every other day.

Examination of the heart revealed the point of maximal impulse to be in the sixth intercostal space at the left mid-clavicular line. The rhythm was grossly irregular at a ventricular rate of 120 per minute. There was a pulse deficit of 10 per minute. The aortic second sound was accentuated and was louder than the pulmonic second sound. No murmurs were audible. The lungs were clear. The veins were not distended. There was no edema. The anterolateral portion of the right fifth rib was exquisitely tender. The blood pressure was 180/100 mm. Hg. A corneal arcus was present bilaterally. Funduscopic examination revealed an increased light streak.

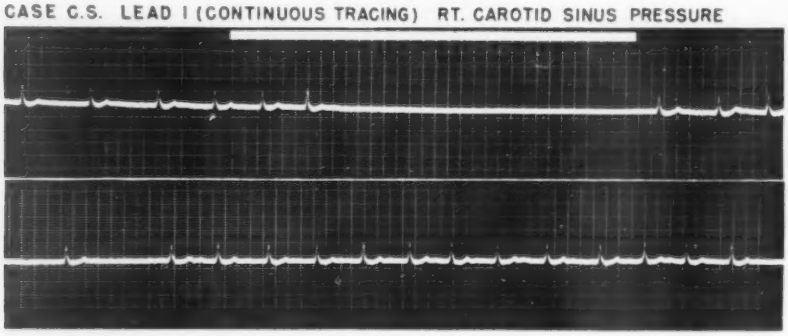

Fig. 2. Case 2. Continuous tracing, lead 1. Initially, there is auricular fibrillation at an average ventricular rate of 75 per minute. Pressure upon the right carotid sinus (white line) results in ventricular standstill. Pressure upon the left carotid sinus produced a similar effect.

Electrocardiographic study disclosed the presence of auricular fibrillation and ST-T alterations consistent with digitalis effect and myocardial disease.

Chest roentgenogram showed an enlarged left ventricle, aortic arch calcification and fracture of the right fifth rib. The blood and urinalysis were normal. The serological tests for syphilis were negative.

Pressure upon the right carotid sinus resulted in ventricular standstill (Fig. 2). No auricular complexes could be identified in any of the electrocardiographic leads. Pressure upon the left carotid sinus resulted in ventricular standstill also. When he complained of dizziness, (which he later volunteered was similar to that which he previously experienced), pressure was released.

Case 3. W. L., a 62-year old white male, was seen in the Cardiac Clinic of Temple University Hospital. He has known of the presence of hypertension for at least 9 years. During the past 6 years, he has been seen regularly at the Clinic because of heart failure. Auricular fibrillation was present for 4 years. During the past 2 or 3 months, he has experienced peculiar episodes of dizziness that appear only in the erect position, standing or walking. On 2 such occasions, he fell. He knew what he was doing but just could not control himself. He never lost consciousness. Examination of the heart revealed the point of maximal impulse to be in the sixth intercostal space at the left anterior axillary line. The rhythm was irregular at a rate of 80 per minute. The aortic second sound was louder than the pulmonic second sound but both were of decreased intensity. No murmurs were audible. The lungs were clear. There was no edema. The blood pressure was 240/120 mm. Hg. Funduscopic examination revealed changes consistent with a grade 2 sclerosis. Chest roentgenogram disclosed an enlarged left ventricle and a tortuous aorta. Electrocardiogram revealed the presence of auricular fibrillation and ST-T alterations consistent with digitalis effect and myocardial disease. Pressure upon the right carotid sinus resulted in neither symptoms nor signs. Pressure upon the left carotid sinus resulted in ventricular standstill and dizziness.

Case 4. P. G., a white male, 81 years old, was admitted to the Episcopal Hospital because of pain located at the apex of the heart. It was dull and aching in character. Pain appeared at rest, 3 days previously. Since then, it has been intermittent and of varying severity. Pain is occasionally associated with

profuse perspiration. He stated that, for many years, he has been short of breath on effort. He is subject to frequent spells of dizziness, particularly on changing from the supine to the erect position.

He has been attending the Cardiac Clinic of Episcopal Hospital since May, 1945. At that time, an electrocardiogram revealed normal sinus rhythm and complete left bundle branch block. In October, 1945, an electrocardiogram revealed auricular fibrillation and complete left bundle branch block. Subsequent electrocardiograms were similar in appearance. He has been taking digitalis (0.1 gm. daily) since 1945, but stopped the drug voluntarily 6 weeks previous to his present hospital admission.

Pressure upon the right carotid sinus produced no effect. Pressure upon the left carotid sinus resulted in the appearance of small ventricular complexes of normal duration occurring regularly at a rate of 28.8 per minute (Fig. 3). The S-T segment became isoelectric and the T waves upright. The corrected Q-T interval during the slow ventricular rate was 0.28. The effects of pressure upon the sinus were reduplicated on several occasions. During the maneuver, the patient stated that he was dizzy.

CASE 5. J. N., a white male, 40 years old, was admitted to the Episcopal Hospital because of hemoptysis, cough and dyspnea. He has known of rheumatic heart disease for 10 years. He has been taking digitalis (0.1 gm. daily) for many years. He has not worked, for the past year, because of shortness of breath. During the past week, shortness of breath increased and hemoptysis and cough became severe. Mercurials were given without relief. Examination revealed a thin white male with orthopnea and cyanosis. The blood pressure was 125/80 mm. Hg. The cervical veins were distended. The point of maximal impulse was in the sixth intercostal space at the left mid-axillary line. The apical impulse was diffuse and heaving. The rhythm was grossly irregular at a ventricular rate of 150 per minute. There was a pulse deficit of 20 per minute. Mitral systolic and presystolic murmurs were present. The second aortic and pulmonic sound were accentuated and equal. There was dulness at the right base with bronchovesicular breath sounds and subcrepitant rales. The liver was enlarged

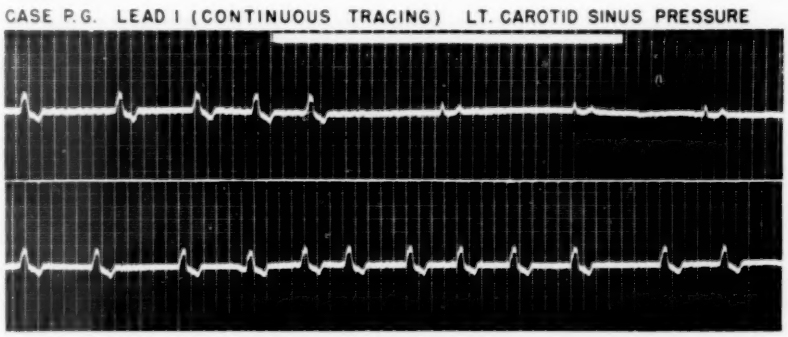

Fig. 3. Case 4. Continuous tracing, lead 1. Initially, there is auricular fibrillation and complete left bundle branch block. The ventricular rate averages 60 per minute. Pressure upon the left carotid sinus (white line) results in the appearance of small QRS complexes, of normal duration, occurring regularly at a rate of 28.8 per minute. Pressure upon the right carotid sinus produced no effect.

Examination on admission revealed a blood pressure of 190/100 mm. Hg. The peripheral arteries were thickened and tortuous. The point of maximal impulse was in the fifth intercostal space, 2 cm. to the left of the left mid-clavicular line. The rhythm was irregular at an average ventricular rate of 80 per minute. There was no pulse deficit. The aortic second sound was accentuated and was louder than the pulmonic second sound. A grade 2, blowing mitral systolic murmur was audible. The lungs were emphysematous. There was no edema. On the first night of hospitalization, pulmonary edema appeared. He was digitalized and improved.

Electrocardiographic study revealed auricular fibrillation and complete left bundle branch block. Chest roentgenogram disclosed slight enlargement of the left ventricle and a tortuous aorta.

and tender. The tip of the spleen was palpable. There was no edema. Chest roentgenogram revealed an enlarged, globular heart and convexity of the left second and third segments. The pulmonary vessels were engorged. The right lower hemithorax was hazy. An electrocardiogram showed auricular fibrillation and changes consistent with combined ventricular hypertrophy, myocardial disease and digitalis effect.

Pressure upon the right carotid sinus produced no effect. Pressure upon the left carotid sinus resulted in an abrupt slowing of the ventricular rate from 135 per minute to 48 per minute (Fig. 4). The ventricular complexes initially increased in size and became regular. There were no symptoms.

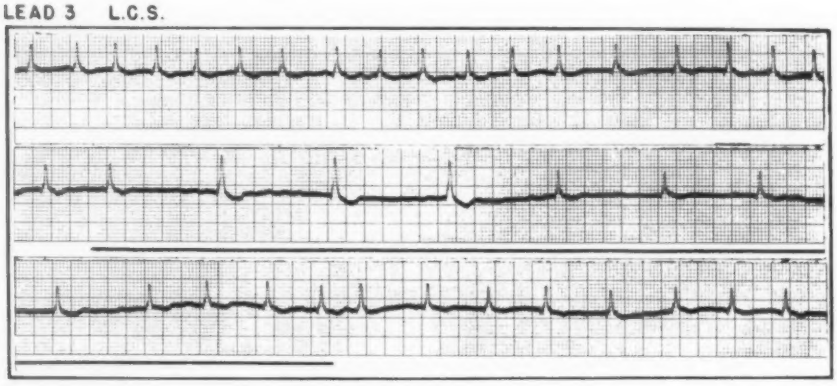

Fig. 4. Case 5. Continuous tracing, lead 3. Initially, there is auricular fibrillation at an average ventricular rate of 135 per minute. Pressure upon the right carotid sinus produced no effect. Pressure upon the left carotid sinus (black line) results in an abrupt slowing of the ventricular rate to 48 per minute. The ventricular complexes are of increased size and regular in rhythm during the initial phase of pressure upon the left carotid sinus.

Case 6. H. M., a 72-year old white male, was admitted to the Episcopal Hospital because of heart failure, progressive in severity during the past 1½ years. The blood pressure was 190/110 mm. Hg. The heart was enlarged to the left anterior axillary line. An irregular rhythm was present at a ventricular rate of 90 per minute. There was a slight pulse deficit. A Grade 1 precordial systolic murmur was audible. The pulmonic second sound was louder than the aortic second sound. Cervical venous distention, pulmonary congestion and marked edema of the lower extremities were present.

The initial electrocardiogram revealed a sinus rhythm, first degree heart block and occasional supraventricular beats. Shortly after admission, he developed auricular fibrillation. Digitalis dosage was increased and mercurials were administered more frequently to restore cardiac compensation.

Pressure upon the right carotid sinus resulted in an abrupt slowing of the ventricular response to a regular rhythm at a rate of 35.7 per minute (Fig. 5). The R wave disappeared but the QRS complex remained of the same duration. The frequency of the auricular complexes did not appear to be changed. No symptoms appeared during carotid sinus massage. Pressure upon the left carotid sinus produced similar results.

Case 7. J. Y., a 69-year old white male, was admitted to the Episcopal Hospital because of weakness and chest pain of 3 weeks' duration. Two years ago, he had an acute myocardial infarction. Since then, he has had occasional cough and shortness of breath on effort. One year ago, he was hospitalized with heart failure. For the past 3 weeks, there has been vague chest discomfort on effort and rest.

Examination of the heart revealed the point of maximal impulse to be in the sixth intercostal space, 11 cm. to the left of the midsternal line. The pulmonic second sound was louder than the aortic second sound. The heart sounds were of decreased intensity. The rhythm was irregular at a rate of 90 per minute. There was a slight pulse deficit. A grade 1 apical systolic murmur was audible. The blood pressure was 180/100 mm. Hg. Funduscopic examination disclosed a grade 2 sclerosis. The cervical veins were slightly

distended. Subcrepitant rales were present in the left lower lobe. The liver edge was palpable and tender. Minimal peripheral edema was present. An electrocardiogram revealed auricular fibrillation and ST-T changes consistent with digitalis effect and myocardial disease.

Pressure upon the right carotid sinus resulted in an abrupt slowing of the ventricular rate from 70 per minute to 44 per minute. The ventricular response became regular. The QRS complex remained of the same duration but changed in configuration from an Rs complex to an R wave of increased magnitude and without either (1) or (2)[24]. The last type has been shown to be a distinct entity and has been differentiated from hysteria by electro-encephalographic study and other methods[5,7,8]. There may be other manifestations such as abnormalities in respiration or in motor function of the gastrointestinal tract[23,24]. When symptoms occur comparable to those experienced spontaneously, the carotid sinus syndrome is said to be present[15].

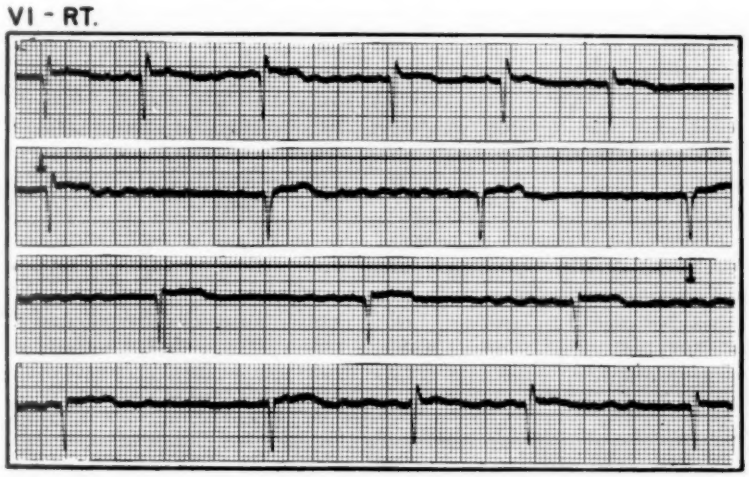

Fig. 5. Case 6. Continuous tracing, lead V_1. Initially, there is auricular fibrillation at an average ventricular rate of 75 per minute. Pressure upon the right carotid sinus (arrow and black line) results in an abrupt slowing of the ventricular response to a regular rhythm at a rate of 35.7 per minute and in a disappearance of the R wave, but the QRS complex is of the same duration. The auricular complexes appear unaltered in frequency.

the T waves became inverted. No symptoms appeared during carotid sinus massage. Pressure upon the left carotid sinus produced similar results.

Discussion. Hyperactive carotid sinus reflexes are usually classified into three types: (1) a cardio-inhibitory type characterized by either an abrupt, significant decrease in cardiac rate or cardiac standstill, interrupted, at times, by nodal escape, (2) a vasomotor type characterized by an abrupt, significant drop in blood pressure and (3) a cerebral type characterized by symptoms

The carotid sinus syndrome is characterized symptomatically by one or more of the following phenomena: syncope, weakness, convulsions, dizziness, roaring in the head hyperventilation, abdominal pain, nausea, vomiting or diarrhea. The most characteristic and frequent attack is that associated with syncope. Common precipitating factors include sudden movement of the head, change in body posture, straining and coughing.

This syndrome must be differentiated from (1) non-reflex cardiac syn-

cope, (2) epilepsy, (3) postural hypotension, (4) Meniere's disease and other causes of syncope. The differential diagnosis is usually quite simple.

The carotid sinus syndrome is more frequently present in the male, in older individuals and in those with heart disease, particularly coronary artery disease and hypertension[20]. The carotid sinus reflex is frequently potentiated by digitalis[16].

Individuals with auricular fibrillation frequently have coronary artery disease, hypertension or both. They, therefore, have the underlying cardiac diseases that are most prone to be associated with a hyperactive carotid sinus reflex. For this reason, we have wondered why the carotid sinus syndrome has not been considered in individuals with auricular fibrillation who have a history of repeated attacks of syncope. Perhaps this syndrome has not been considered in those with this arrhythmia because (1) carotid sinus pressure has converted sinus rhythm in some individuals to auricular fibrillation[24], (2) experimental vagal stimulation has converted sinus tachycardia to auricular fibrillation[11,18], (3) the assumption that vagotonia is already present in individuals with auricular fibrillation and that the naturally varying ventricular rate is an expression partly of the waxing and waning of vagal tone[1,12,14,22] and (4) the belief that the hyperactive carotid sinus reflex is of highest incidence in those with normal or slightly decreased heart rates[19].

The hyperactive carotid sinus reflex of the cardio-inhibitory type may be induced by either (1) exaggerated stimuli to the carotid sinus receptors, the afferent nerves or the central synapse in the medulla, or (2) an exaggerated response of the heart to the efferent arc. Direct vagal control of the heart in man involves principally the auricles[2]. The vagus nerve is thought to have but slight direct influence over the ventricles. However, Linenthal has recently presented electrocardiographic observations indicating that the effect of carotid sinus pressure in a 70-year old man with coronary artery disease was either upon the intrinsic cardiac nerves to the auriculo-ventricular node or directly upon the node[13]. Peterson has also suggested a direct vagal control of the ventricles[17].

The following observations would appear to indicate that the predominant effect of carotid sinus pressure in our patients was upon the auriculo-ventricular node: (1) persistence of auricular fibrillation and abolition of the ventricular response, (2) persistence of auricular fibrillation and the development of a slower but now regular ventricular response (auricular fibrillation and complete heart block)[9], (3) disappearance of ventricular ectopic beats if the ventricular rate was significantly decreased, and the persistence of ventricular ectopic beats if the ventricular rate was insignificantly decreased, and (4) the appearance of QRS complexes of normal duration at regular intervals but at a slower rate in an individual with complete left bundle branch block of 9 years' duration. These observations confirm the suggestions of others that the intensity of the carotid sinus reflex is intimately related to the sensitivity of the end-organ[15,20]. Frequently, a history of the usual precipitating factors that initiate the carotid sinus syndrome cannot be elicited[21]. Perhaps a sudden decrease in myocardial function may be the trigger mechanism in these patients.

It is important to recognize this syndrome because it alarms the sufferer and yet does not have as serious a prognosis as do the other types of cardiac syncope. Furthermore, therapy may be effective in preventing recurrent attacks.

We believe therapy should be directed toward (1) increasing myocardial efficiency and (2) blocking the reflex arc somewhere in its course. Although digitalis increases the sensitivity of the carotid sinus reflex, its salutary effect on cardiac efficiency far outweighs this undesirable effect and it should, therefore, be used in optimal dosage, if indicated. Vagal blocking drugs are most useful in attempting to break the reflex arc[4,6] but are frequently ineffective[10]. Finally, conversion to a normal sinus rhythm may be attempted but in our hands, unfortunately, we have not been able, with quinidine sulfate, to establish sinus rhythm in the majority of these individuals with advanced heart disease.

Summary and Conclusions. 1. A hyperactive carotid sinus reflex of the cardio-inhibitory type is described in 7 of 20 consecutive individuals with auricular fibrillation.

2. In 3, each with a history of syncope, ventricular standstill occurred. In the other 4, 2 of whom had a history of recurrent episodes of dizziness and lightheadedness, the ventricular response was abruptly and significantly slowed and became regular.

3. The auricular complexes appeared to be unchanged in frequency. The QRS complex became larger in 2, an R wave was abolished in one, and, in another, the configuration of complete left bundle branch block of 9 years' duration was transformed to that of normal conduction.

4. The predominant effect of carotid sinus pressure in these individuals appears to be upon the auriculoventricular node.

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CORRELATION BETWEEN ACTIVE RHEUMATIC LESIONS IN THE LEFT AURICULAR APPENDAGE AND ELSEWHERE IN THE HEART

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The frequent occurrence of Aschoff bodies in the left auricular appendages of patients subjected to mitral commissurotomy for mitral stenosis has been amply documented[1,2,4,5,6]. In the selection of patients for operation, one of the criteria used has been the absence of clinical evidence of rheumatic activity. The finding of Aschoff bodies had, therefore, been unexpected and has given rise to questions as to its meaning. The most important of these relates to the significance of this morphologic evidence of activity with respect to the patient's long time prognosis and its bearing on the ultimate success or failure of valve splitting procedures. This will only be answered by longer post-operative periods of observation than are presently possible. A second question, however, one which perhaps bears some relation to the first, is whether the activity in the auricular appendage is an isolated phenomenon or does it reflect activity elsewhere in the heart. It is to this latter problem that this study has been addressed.

Materials and Methods. The hearts of 40 patients were available for study. Twenty of these were museum specimens chosen and preserved for teaching purposes. These had been selected as cases demonstrating the characteristic gross pathologic changes of rheumatic heart disease. Fifteen represented consecutive unselected cases of rheumatic heart disease encountered in the routine necropsy material at Bellevue Hospital. Five were cases of mitral stenosis upon whom commissurotomy had been performed and who died following operation.

In all cases sections were taken from the tip of the left auricular appendage. In the post-operative group, sections of appendage taken at the time of commissurotomy as well as additional necropsy specimens were available. The museum specimens had been preserved in Kaiserling's solution. These were washed and refixed in Zenker's solution. All other specimens were fixed directly in Zenker's solution. Multiple sections of left ventricular wall, septum, auricle, involved valves and, in some cases, right ventricular wall were available for study. All sections were embedded in paraffin in the usual fashion, sectioned, and stained with hematoxylin and eosin.

The lesions assumed to be active were subendocardial or myocardial Aschoff bodies, verrucous endocarditis of valves, and the characteristic auriculitis of the posterior wall of the left atrium.

Results. The presence or absence of morphologic evidences of activity in the 40 cases together with some of the pertinent clinical data where available are listed in Table I. Although some of the clinical data would seem to be suggestive of activity in cases judged clinically inactive, the influence of such factors as other intercurrent infections on this judgment has not been indicated. The classification of cases as clinically active or inactive was dependent upon the final clinical im-

pression in which presumably all such factors were taken into consideration together with the total clinical picture. Since we have been unable to identify active lesions in thrombosed appendages, the presence or absence of thrombi may well affect the incidence of lesions in this site and have, therefore, been included in the chart.

In 9 cases, Aschoff bodies were found in the left auricular appendage. In all of these, evidences of activity were found elsewhere in the heart in the form of ventricular myocardial Aschoff bodies, verrucous endocarditis of valves, auriculitis, or combinations of these three lesions. In 6 cases the appendages were negative but active lesions were found at other sites. Three of these negative appendages in active cases contained organized thrombi.

Five of the 40 cases were considered active clinically and so designated in the final diagnosis prior to necropsy. Four had lesions in the left appendage as well as lesions in the ventricular myocardium and valves. In the fifth, the appendage was thrombosed but there was a striking verrucous tricuspid valvulitis.

The presence of thrombi in various stages of organization in the left auricular appendage appears to be closely related to rhythmic abnormalities. Thus of the 18 cases with thrombosed left appendages, 17 had auricular fibrillation and one had auricular flutter. Four patients with fibrillation and one with auricular flutter were free of thrombi.

Comment. Cases in which commissurotomy has been performed at Bellevue Hospital now number 28. Of these, 14 have had Aschoff bodies in the biopsied left auricular appendage. This 50% incidence is comparable to what has been found in other reported series[1,2,4,5,6]. It was this high incidence of active lesions and the ease with which they were found that led us to believe that the left auricular appendage might be a favored site for their formation. This does not seem to be borne out by the present necropsy series for in all cases in which Aschoff bodies were found in the left appendage, evidences of activity were found elsewhere in the heart and in sites from which sections are ordinarily taken. The reverse is not true, however, for in 6 cases the appendage was negative although verrucous endocarditis of valves was present in 4 and Aschoff bodies were found in the ventricular myocardium of the other 2. This experience would seem to indicate that the presence of active lesions in the left auricular appendage makes it very likely that active lesions may be expected elsewhere in the heart. The absence of lesions in the left appendage does not preclude the possibility of areas of activity at other sites.

Pinniger[5] has reported one case in which Aschoff bodies were found in the biopsied left appendage and in which subsequent necropsy revealed active auriculitis and ventricular myocarditis. Ellis and associates[3], however, note that they have seen several cases in which necropsy failed to reveal other active cardiac lesions although the biopsied left appendages had contained Aschoff bodies.

In only 5 of the 35 clinically inactive cases were Aschoff bodies found in the left auricular appendage. This is a much lower incidence than that seen in appendages biopsied during mitral commissurotomy. It should be noted, however, that the necropsy cases, with the exception of the post-operative deaths, represent patients at the very end stage of the natural evolution of the disease. Perhaps even more significant is the fact that the age range in the necropsy series is much wider and includes many more older individuals

TABLE 1.—CLINICAL AND PATHOLOGICAL ACTIVITY IN FORTY NECROPSIED CASES OF RHEUMATIC HEART DISEASE

			Rheumatic activity			*Clinical data during terminal illness*[2]				
			Pathological							
Case No.	*Age*	*Sex*	*L. auricular appendage*[1]	*Other sites in heart*	*Clinical impression*	*Joints*	*Temp.*	*E.C.G. abnormalities*	*ESR*	*WBC*
1.	8	F	Active	Active (valvulitis, myocarditis, auriculitis)	Active	+	102.4	—	30	10,800
2.	7	F	Active	Active (valvulitis, myocarditis, auriculitis)	Active	0	100	P.R. = 0.18	35	9,800
3.	4	F	Active	Active (valvulitis, myocarditis)	Active	+	104.3	P.R. = 0.17	36	18,000
4.	19	M	Active	Active (valvulitis, myocarditis)	Active	+	102	Rt. B.B.B.[3]	123	20,200
5.	45	M	Active	Active (valvulitis, myocarditis, auriculitis)	Inactive	0	101.6	Lt. B.B.B.[3]	35	7,450
6.	60	F	Active	Active (valvulitis)	Inactive	0	97	Aur. flutter	39	5,400
7.	47	F	Active	Active (myocarditis)	Inactive	0	101	Lt. B.B.B.[3]	18	8,700
8.	26	F	Active	Active (myocarditis, auriculitis)	Inactive	0	99	Wandering pacemaker	10	7,800
9.	42	M	Active	Active (myocarditis)	Inactive	0	100	None	14	11,000
10.	37	M	Inactive (thrombosed)	Active (valvulitis)	Active	0	100	Aur. fibrillation	56	17,100
11.	26	M	Inactive (thrombosed)	Active (myocarditis)	Inactive	0	100.6	Aur. fibrillation	—	6,900
12.	52	F	Inactive (thrombosed)	Active (valvulitis)	Inactive	0	101.4	Aur. fibrillation	20	24,500
13.	64	M	Inactive	Active (myocarditis)	Inactive	0	97	Aur. fibrillation	44	7,200
14.	45	F	Inactive	Active (valvulitis)	Inactive	0	101.2	None	12	13,650
15.	48	F	Inactive	Active (valvulitis)	Inactive	0	98.6	—	—	—
16.	56	M	Inactive	Inactive	Inactive	0	99.2	None	—	—
17.	36	M	Inactive (thrombosed)	Inactive	Inactive	0	98.6	Aur. fibrillation	—	—
18.	60	M	Inactive	Inactive	Inactive	0	98.6	Aur. fibrillation	—	6,800
19.	64	F	Inactive	Inactive	Inactive	0	97	A.v. nodal rhythm	—	10,800
20.	45	M	Inactive (thrombosed)	Inactive	Inactive	0	99	Aur. fibrillation	—	—

TABLE 1. (*Continued*)

Case No.	Age	Sex	Rheumatic activity: Pathological: L. auricular appendage[1]	Rheumatic activity: Pathological: Other sites in heart	Rheumatic activity: Clinical impression	Clinical data during terminal illness[2]: Joints	Temp.	E.C.G. abnormalities	ESR	WBC
21.	38	F	Inactive (thrombosed)	Inactive	Inactive	0	99.4	Aur. fibrillation	22	21,500
22.	30	M	Inactive (thrombosed)	Inactive	Inactive	0	101.4	Aur. fibrillation	11	8,300
23.	58	F	Inactive (thrombosed)	Inactive	Inactive	0	99.6	Aur. fibrillation	—	6,300
24.	25	M	Inactive	Inactive	Inactive	0	97.6	—	—	—
25.	30	F	Inactive	Inactive	Inactive	0	102	None	—	10,500
26.	64	F	Inactive	Inactive	Inactive	0	98.6	None	—	—
27.	32	M	Inactive	Inactive	Inactive	0	98.2	None	—	—
28.	43	M	Inactive-(thrombosed)	Inactive	Inactive	0	98	Aur. fibrillation	—	4,450
29.	54	F	Inactive (thrombosed)	Inactive	Inactive	0	99.4	Aur. fibrillation	—	9,700
30.	73	F	Inactive (thrombosed)	Inactive	Inactive	0	99.8	Aur. fibrillation	—	13,000
31.	52	F	Inactive (thrombosed)	Inactive	Inactive	0	98	Aur. fibrillation	—	51,000[4]
32.	63	F	Inactive	Inactive	Inactive	0	99	Aur. fibrillation	—	8,900
33.	26	F	Inactive (thrombosed)	Inactive	Inactive	0	99.6	Aur. fibrillation	—	21,800
34.	48	F	Inactive (thrombosed)	Inactive	Inactive	0	100	Aur. fibrillation	50	20,000
35.	41	M	Inactive	Inactive	Inactive	0	98	Aur. fibrillation	39	7,750
36.	54	M	Inactive (thrombosed)	Inactive	Inactive	0	100	Aur. fibrillation	—	7,550
37.	37	F	Inactive (thrombosed)	Inactive	Inactive	0	99.8	Aur. fibrillation	15	9,000
38.	59	F	Inactive (thrombosed)	Inactive	Inactive	0	100	Aur. flutter	—	8,600
39.	35	F	Inactive (thrombosed)	Inactive	Inactive	0	98.4	Aur. fibrillation	23	10,500
40.	34	M	Inactive	Inactive	Inactive	0	99.4	None	10	12,100

[1] "Active" indicates presence of subendocardial Aschoff bodies
[2] Temp., E.S.R. and W.B.C. are highest recorded during terminal illness
[3] Bundle Branch Block
[4] Leukemoid reaction following radiation therapy for carcinoma of cervix

than do any of the reported operative series.

In the preceding discussion we have assumed that verrucous endocarditis of valves or Aschoff bodies are evidences of rheumatic activity. There is little question as to the significance of the former but some doubt as to the meaning of the latter. In a group of cases of typical rheumatic heart disease, there seems to be little point to arguing the specificity of Aschoff bodies. The important consideration would appear to be the recognition of the fact that the Aschoff body is an inflammatory reaction and one which, in healing, often leaves a residual scar. The occurrence of such a lesion, then, must be included in any definition of pathologic activity. In general, the extent and frequency of Aschoff bodies has varied directly with the severity of the clinical manifestations of disease and in this series, with one exception, they were most frequent and most widespread both in the left appendage and in the remainder of the heart in those cases in which the unequivocal clinical diagnosis of active rheumatic heart disease was made.

The presumption that Aschoff bodies are evidence of activity does not permit us to predict that patients with this lesion in the left appendage will eventually do poorly. It should be noted that in clinically inactive cases with positive left appendages, Aschoff bodies in other sites in the heart were usually few in number. As Pinniger[5] has pointed out, we do not as yet understand how the Aschoff body, a lesion of the interstitial connective tissue, affects myocardial function.

Verrucous valvulitis would seem to be more serious in its prognostic implications and was found in 6 of the 9 cases with active lesions in the left auricular appendage and in 4 of the 6 active cases without appendageal lesions. In no instance, however, could we identify active endocarditis superimposed on a scarred or calcified, severely deformed mitral valve. This lesion was found in valves which were the site of lesser degrees of old damage or showed no evidences of earlier involvement.

As indicated above, the presence or absence of thrombi in the left auricular appendage seemed to be dependent upon abnormalities of rhythm and in particular upon auricular fibrillation. Employing the presence of Aschoff bodies as the sole criterion of activity in this location, we were unable to demonstrate activity in the appendage beneath thrombi. While it is true that the non-specific infiltration of lymphocytes and mononuclear cells beneath an organized or organizing thrombus may confuse the picture, it is noteworthy that of the 18 cases with thrombi, only 4 showed evidences of activity anywhere in the heart and 14 were totally inactive.

Summary. In 40 rheumatic hearts examined at necropsy, 9 left auricular appendages contained subendocardial Aschoff bodies. All of these 9 cases had active lesions in other locations in the heart. Six of the 40 hearts had evidences of activity in other areas although the left auricular appendages were inactive. The presence of rheumatic activity in the left appendage would seem to indicate that lesions are very likely to be present elsewhere in the heart. The absence of Aschoff bodies in the left appendage does not preclude the possibility of activity at other sites in the heart.

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EFFECTS OF RENIN IN RATS PRETREATED WITH HYDROCORTISONE AND SOMATOTROPHIN*

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Subcutaneous administration of a kidney extract containing renin to uninephrectomized rats pretreated with desoxycorticosterone acetate (DCA) and salt (1% NaCl as drinking fluid) precipitates an eclampsia-like syndrome with massive edema, oliguria, hypertension, nervous symptoms and death[5]. At necropsy, these animals demonstrate widespread visceral hemorrhages and severe acute renal and extrarenal vascular lesions[6]. Under identical conditions, cortisone sensitizes to a symptomatically similar effect of renin; this condition differs quantitatively from that due to DCA in that hemorrhages are less severe and lesions of splanchnic vessels are more intense[7]. Thus, 2 synthetic steroids with different, and in some respects reciprocal properties, are alike in that they sensitize to a vasculotoxic property of renin.

It was, therefore, of interest to determine whether or not hydrocortisone, which is cortisone-like and which is a major constituent of natural adrenal cortical secretions, would also have this property. Further, somatotrophin is believed to stimulate liberation of desoxycorticosterone-like compounds from the adrenals[9], so that pretreatment with this substance should have the effect of DCA. The present report deals with the effects of hydrocortisone and somatotrophin pretreatment on the reaction to subcutaneous renin.

Procedure. General experimental conditions were the same as those in prior studies on DCA and cortisone[5,7]: The rats were female, uninephrectomized, averaged about 120 gm. body weight, were fed Purina fox chow and given 1% NaCl as drinking fluid.

The grouping of the experiments is shown in Table 1. Two groups were given hydrocortisone and renin, one hydrocortisone alone, one somatotrophin and renin, and one renin alone while another served as absolute control. The longer interval of pretreatment and larger renin dose used in Group II stemmed from an attempt to induce the postrenin edema observed with DCA and cortisone but unexpectedly absent in Group I. Somatotrophin and renin-control series were similarly treated with the aim of inducing maximum effects.

Hydrocortisone acetate (Hydrocortone, Merck, saline suspension) was given in single daily subcutaneous doses of 2.5 mg. Somatotrophin suspension was prepared from a powder by mixing it in a water solution containing 1% NaCl and 10% ethanol. This suspension was prepared semiweekly and was kept at 4° C; it was injected in 2 daily doses of 0.2 cc. which corresponded to 12.5 units of stated activity.

Arterial pressures were measured regularly during pretreatment periods in animals of

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Groups I, IV and VI by the objective tail method of del Greco *et al.*[2]. On the last day of this period, the animals were placed in metabolism cages for study of the effect of renin on fluid balance.

The renin was that used in prior studies[6]; it had a potency of 56 Goldblatt dog units per cc. It was given in 2 daily doses of 0.25 cc. each for 3 days in Group I and in 3 daily doses of 0.5 cc. each for 3 days in Groups II, III and V.

The animals of all groups were sacrificed on the 4th day after the start of renin treatment in test groups; animals of Groups II, III and V were exsanguinated under ether and blood obtained for chemical analysis. All the animals were necropsied and tissues fixed in Zenker's fluid; the tissues selected for study were then weighed, sectioned and stained with hematoxylin-eosin-methylene blue (H and E), periodic acid-fuchsin (PAS), trichrome and phosphotungstic acid hematoxylin (PTA).

Results. FUNCTIONAL. As expected hydrocortisone suppressed and somatotrophin accelerated growth (Table 2). Hydrocortisone increased the means of blood pressures; the values observed in the last 3 prerenin days were 164 (range 115 to 180) in Group I, and 167 (range 135 to 182) in Group IV; the control showed a mean of 137 mm. Hg (range 120 to 148).

Fluid exchange was observed in terms of urine flow and abrupt changes in body weight. In the prerenin periods,

TABLE 1.—TREATMENT AND URINE FLOW IN VARIOUS GROUPS

Group	*No. of animals*	*Pretreatment*		*Renin daily dose in cc.*	*Urine flow in cc. per 24 hrs.*
		Nature	*Days*		
I	10	Hydrocortisone	20	0.5	96 (15—202)
II	8	Hydrocortisone	26	1.5	95 (35—260)
III	8	Somatotrophin	26	1.5	52 (30—79)
IV	8	Hydrocortisone	20	0	10 (8—12)
V	8	0	26	1.5	84 (72—103)
VI	5	0	20	0	17 (10—22)

TABLE 2. FUNCTIONAL AND CHEMICAL EFFECTS OF RENIN IN RATS PRETREATED WITH HYDROCORTISONE OR SOMATOTROPHIN

Group and treatment	*Body weight in gm.*		*Hemoglobin gm.%*	*Serum chlorides mEq./L.*	*Serum sodium mEq./L.*	*Serum urea nitrogen mg./100cc.*
	*A.**	*P.**				
II Hydrocortisone + Renin	106 88–120	102 81–145	13.2 12.2–14.7	100 88–109	125.5**	39.3 28–50
III Somatotrophin + Renin	192 169–205	200 162–220	13.5 12.4–15.2	109 103–114	128 124.5–140	35 28.3–50.5
V No Pretreatment + Renin	150 120–160	155 122–168	13.4 12.1–14.8	110 107–113	127 123.5–131	32.4 25–40.7

* Before (*A*) and after (*P*) renin treatment
** Determination on pooled samples

neither hydrocortisone nor somatotrophin altered urine flow. Subsequent administration of renin progressively increased urine flow in all treated groups (Table 1). Animals pretreated with cortisone or DCA show sharp gains of body weight and edema during the period of renin administration[5,7]; in contrast, such occurred only in one animal of Group II and in none of either Group I or Group III. In further contrast to the DCA-renin studies, neither hydrocortisone plus renin nor somatotrophin plus renin caused increases in the serum concentrations of Na or Cl or resulted in severe azotemia (Table 2). Neither somatotrophin plus renin nor renin alone decreased serum K concentration which in these Groups (III and V) averaged 4.1 mEq. per liter.

Renin elicited no severe constitutional symptoms in animals of Groups I and III; 3 animals of Group II died during renin administration; 2 of these were cachectic (body weight losses of 50 gm.) and succumbed to massive lung abscesses; the other was the animal in which renin elicited a gain in weight from 95 to 145 gm.

MORPHOLOGICAL. A. *Gross.* Two animals given hydrocortisone alone showed small lung abscesses. Among the 18 given hydrocortisone plus renin, 8 showed lung abscesses, 14 visceral hemorrhages, 5 accumulations of pleural and/or ascitic fluid and 1 intussusception; there was no gross distinction in the severity of these lesions as between Groups I and II.

Organ weights were measured in animals of Groups II, III and V and are summarized in Table 3. As expected, hydrocortisone or hydrocortisone plus renin caused atrophy of thymus, spleen and adrenals, whereas somatotrophin neither decreased nor increased measured organ weights. The thymic and adrenal responses to somatotrophin indicate that its effect on the adrenals is not associated with hypersecretion of 11-oxy-corticosteroids.

TABLE 3.—MORPHOLOGIC EFFECTS OF RENIN IN RATS PRETREATED WITH HYDROCORTISONE OR SOMATOTROPHIN

Group and treatment	*Thymus*	*Spleen*	*Kidney*	*Heart*	*Adrenals*
II Hydrocortisone	A*	240	830	360	14
+		100–450	520–1430	190–470	11–18
Renin					
III Somatotrophin	188	750	790	370	38
+	139–324	120–1290	500–1320	270–640	26–63
Renin					
V No Pretreatment	123	640	620	290	22
+	91–154	530–770	590–670	260–320	20–25
Renin					

All organ weights are in mg. expressed in percentage of body weight
* Atrophic, not measurable

B. *Microscopic.* The lesions provoked by hydrocortisone alone or by somatotrophin plus renin were limited to the kidney and were unimpressive. Hydrocortisone caused the appearance of focal hyaline droplets in cells of scattered glomerular tufts and of minor irregularities in basement membrane structure; cortisone elicits similar lesions[3,7]. The somatotrophin plus renin treatment caused only the hypertrophy of nephrons and irregular intensification of basement membrane structure which would be expected from somatotrophin alone (Fig. 1).

The lesions elicited by giving renin to hydrocortisone-pretreated rats correspond to those obtained with corti-

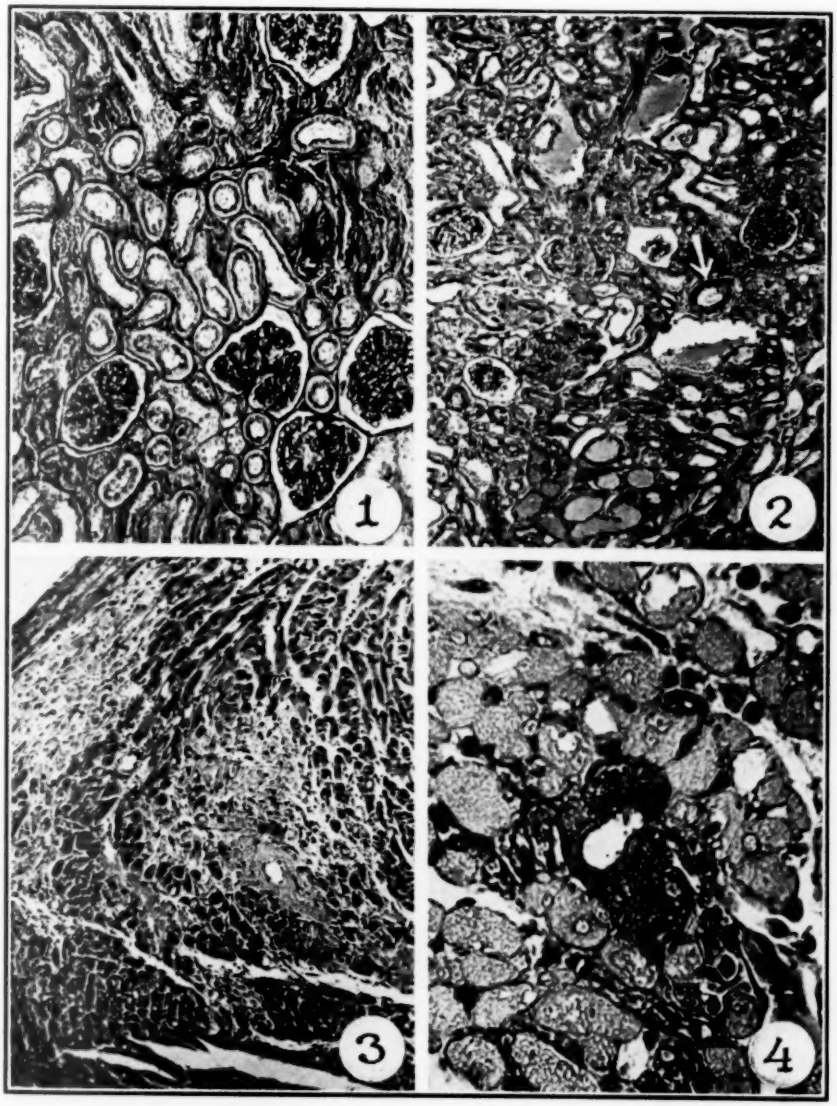
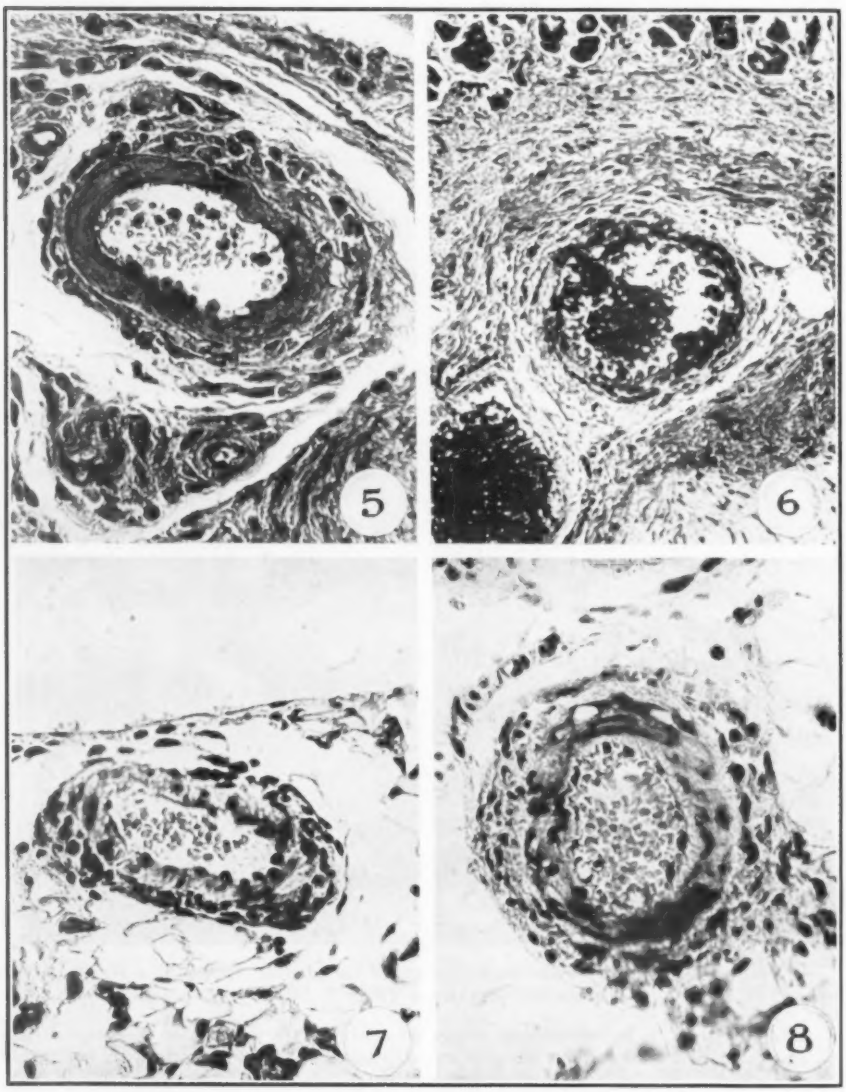


Fig. 1. – Nephron hypertrophy with intensification of membrane outline in a rat given somatotrophin plus renin (PAS × 145).

Fig. 2. – Renal effects of hydrocortisone plus renin: irregularly distributed glomerular degeneration, cast formation with tubular atrophy and dilatation and (arrow) arteriolar hyalinization (PAS × 100).

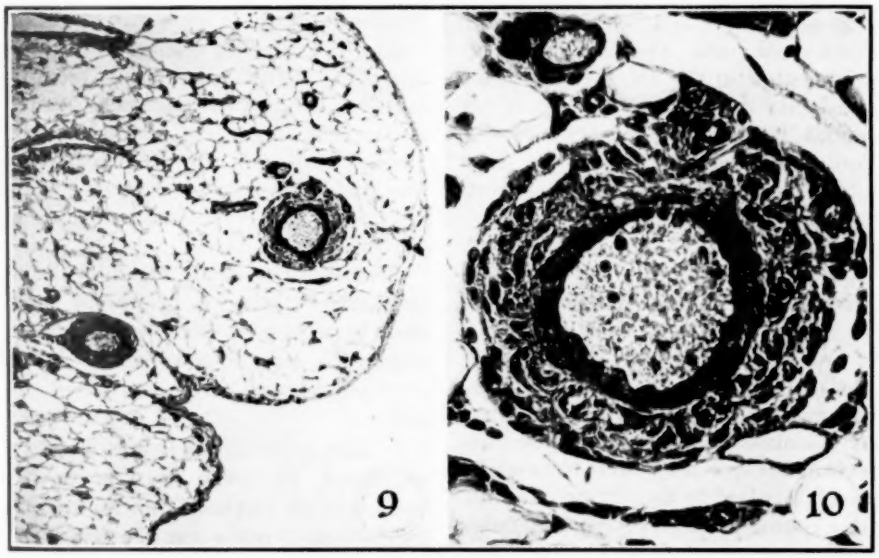
Figs. 3 (H and E × 110) and 4 (PAS × 620). – Myocardial lesions due to hydrocortisone plus renin. Dilatation of terminal vessels with perivascular hyaline infiltrate and necrosis of involved myocardial fibers.

sone and renin[7]. They manifested themselves in kidneys, heart and the intestinal tract. The renal lesions involved glomeruli, tubules and arterial vessels; the glomeruli showed irregularly distributed hyaline degeneration, atrophy and swelling of basement membranes and focal capillary thrombosis; the tubules were diffusely dilated, atrophic and filled with granular hyaline de-



Figs. 5, 6, 7, 8. – Arteriolar effects of hydrocortisone plus renin: Fig. 5, medial hyalinization and loss of folding of elastica (stomach, PAS × 525); Fig. 6, intimal extrusion of medial fibrinoid deposits (PTA × 500); Figs. 7 and 8 (mesentery, H and E × 450) represent stages of medial degeneration with (7) necrosis and (8) vacuolization and nuclear swelling and irregularity.

posits. The small renal arteries exhibited medial hyalinization (Fig. 2). Similar hyalinization occurred in larger myocardial arterioles while what seemed to be their terminal segments were dilated; these dilated vessels were surrounded by an amorphous deposit which suffused between the muscle fibers; the affected muscle fibers became degenerate and necrotic (Figs. 3 and 4). The small intestinal arteries showed marked vacuolization of the media, distortion and degeneration of muscle fibers and their nuclei (Figs. 7 and 8) and, unexpectedly, adventitial cuffing which consisted of fibroblastic proliferation and occasionally of lymphocytic infiltration (Figs. 9 and 10). As in the heart, terminal vessels in the intestinal mucosa were dilated and involved in amorphous deposits, hemorrhage and necrosis. The musculature



Figs. 9 and 10. – (PAS, mesentery, respectively × 100 and × 525) Medial hyalinization with fibroblastic cuffing due to hydrocortisone plus renin.

and large arterioles were severely affected by medial hyalinization, as shown by the PAS stain, and by medial fibrinoid deposits (Figs. 5 and 6). The latter, with the phosphotungstic stain, appeared as blue streaks against the background of orange media; the elastica of these vessels was stretched, and the intima of some distorted by subintimal accumulations of what seemed to be extruded medial fibrinoid; the endothelium over and near these deposits appeared swollen. Mesenteric vessels were similarly affected; some of the intestine in the region of these diseased vessels showed, in some sections, ill-defined dark bluish streaks which probably represent dispersed nuclear material and an initial phase of muscle fiber necrosis.

Discussion. The above experiments add another to the group of states such as nephrectomy[8], pretreatment with DCA[6] or cortisone[7], which sensitize to the action of renin and result in fulminant vascular lesions. In all of these, administration of excess sodium is a basic conditioning factor. Subcutan-

eously administered renin, which is relatively harmless in normal dogs or rats, becomes severely injurious in sensitized animals. Since the angiotoxic effects of renin are evident only in dogs with total or subtotal renal insufficiency, and since the syndrome elicited by DCA plus renin involves a state of oliguria and renal failure, it would seem that uremia is another important sensitizing factor. This, however, is not the case; the disease elicited by the combination hydrocortisone + renin is not associated with uremia or oliguria. The acute fluid retention noted in the DCA or cortisone treated rats injected with renin is not essential to the development of the lesions since edema was rarely seen in the hydrocortisone-renin experiment, while lesions were present in all the animals.

The mode of action of the basic sensitizing factors (adrenal steroids and salt) is obscure; presumably these factors are associated with abnormalities in the distribution of sodium in tissues. It seems likely that arteries and arterioles maintained in a state of sodium repletion become sensitized to vascular damage incident to the action of renin. This hypothesis presupposes interplay of the effects of renin and sodium ion. Such an interplay is illustrated in the 2 following observations: (a) renin diuresis is enhanced by administration of isotonic saline[1], and (b) the syndrome which results from cortisone + renin + salt, is absent if isotonic saline is replaced by distilled water at the time of renin injections[7]. Thus, the experiments point towards the possibility that renal and adrenal factors in the presence of salt can operate together in the genesis of several forms of fulminant vascular disease.

Among other observations is the fibroblastic vascular cuffing which occurred around degenerating arterioles in rats treated with hydrocortisone; a similar phenomenon has also been described in rats treated with cortisone and salt[10]. It is of interest, because it contrasts with the prompt resolution of inflammatory perivascular exudates caused by these steroids in rats with experimental DCA hypertensive disease[1].

Lastly, failure to elicit an eclampsia-like state in rats given somatotrophin and renin indicates that somatotrophin does not under these conditions elicit an outpouring of desoxycorticosterone-like adrenal steroids comparable to that obtained from subcutaneously implanted DCA pellets.

Summary. 1. Acute vascular lesions resembling those of fulminant malignant hypertension are elicited by subcutaneous injections of renin in rats pretreated with hydrocortisone and salt.

2. This state differs from that of rats sensitized to renin by desoxycorticosterone or cortisone pretreatment in that edema is not a common manifestation.

3. Somatotrophin pretreatment did not have the renin-sensitizing effect of desoxycorticosterone, cortisone or hydrocortisone.

4. These observations suggest a relationship between induced abnormalities of sodium distribution, presumably intracellular, and the susceptibility of vessels to a necrotizing effect of the subcutaneously injected renin.

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EFFECT OF ACTH ON THE EOSINOPHIL COUNT IN PERIPHERAL BLOOD AND BONE MARROW*

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It has been shown repeatedly that the administration of ACTH or of cortisone may produce a decrease in the circulating eosinophils. It has not been shown how this decrease is brought about. Some of the possible mechanisms which might be involved are: (1) destruction of the peripheral eosinophils, (2) a decreased rate of release of the eosinophils from the bone marrow, (3) a decreased rate of maturation of the marrow eosinophils, or (4) sequestration of circulating eosinophils in the liver, spleen, bone marrow, or other tissues.

If the maturation rate of eosinophils is decreased, or their release from the bone marrow is interfered with, or they are sequestered in the marrow, it should be possible to show a change in the number of marrow eosinophils following the administration of ACTH or cortisone.

Since the eosinopenia in the peripheral blood occurs very rapidly, one might expect an equally rapid alteration in the cytology of the bone marrow, if this were the primary site of the essential change in the rate of eosinophil formation or removal.

The present study was done to compare the immediate effect of ACTH on the marrow with that on peripheral blood.

Method. Twelve patients were studied who had eosinophils in the blood ranging from 3.00% to 16.7%. The eosinophil counts were performed according to Randolph's method[8]. These counts were made by diluting peripheral blood with Randolph's fluid and counting 1000 white blood cells in a standard counting chamber. The absolute number of eosinophils was obtained by multiplying the per cent of eosinophils by the total white cell count obtained on the same preparation. All the patients except one had some form of malignant neoplasm. The one exception was a patient with eosinophilic granuloma of bone. Of those with neoplasms, there was no evidence of widespread marrow involvement except in one patient who had Ewing's tumor. Cellular marrow specimens were obtained in all cases. Clinical evidence of allergy was not present, although some of the patients had an eosinophilia believed to be due to reaction to neoplasm.

The ACTH was given by both the intramuscular and intravenous routes. Five patients were given 25 mg. of ACTH intramuscularly. Bone marrow aspirations from

* Study made possible under contract with the United States Atomic Energy Commission.

TABLE 1.—PERIPHERAL BLOOD EOSINOPHILS AND MARROW CELLS BEFORE AND AFTER INTRAVENOUS ACTH

1. Patient	*G.F.*		*R.G.*		*R.H.*		*C.C.*		*H.R.*		*W.A.*		*D.J.*	
	Before ACTH	*After ACTH*	*Before ACTH*	*After ACTH*	*Before ACTH*	*After ACTH*	*Before ACTH*	*After ACTH*	*Before ACTH*	*After ACTH*	*Before ACTH*	*After ACTH*	*Before ACTH*	*After ACTH*
2. Blood Eosinophils/mm³ by chamber count	370	87	1082	60	588	92	273	0	612	187	153	32	415	134
3. Marrow cell types/1000 cells counted:														
Myeloblasts	0	0	0	0	3	1	2	0	1	1	2	0	4	0
Promyelocytes	7	20	13	12	22	23	15	10	8	10	17	19	33	10
Myelocytes	154	138	78	33	135	224	128	142	103	105	126	92	104	112
Metamyelocytes	108	139	88	62	116	100	114	107	125	130	143	80	102	116
Neutrophils Band	161	142	82	110	175	88	116	146	218	183	139	96	148	206
Neutrophils Segmented	140	112	118	160	74	57	164	158	101	77	117	159	103	102
Eosinophil Myelocytes	11	22	13	19	14	13	14	10	16	17	5	19	23	10
Eosinophil Metamyelocytes	11	10	5	8	9	16	8	10	7	11	6	10	11	11
Eosinophils Band	13	15	10	11	16	13	10	5	10	19	4	4	27	12
Eosinophils Segmented	30	5	24	19	14	13	18	11	16	17	12	15	20	22
Basophils	1	4	3	2	3	1	1	2	5	2	0	5	5	4
Erythroblasts	5	2	6	10	14	10	6	9	4	5	5	10	4	10
Early Normoblasts	24	26	77	46	33	32	26	35	18	15	29	74	24	15
Intermediate Normoblasts	82	107	147	173	86	88	123	111	70	71	102	140	91	91
Late Normoblasts	143	155	177	170	177	152	156	131	164	174	226	210	152	151
Megakaryocytes	0	3	3	0	2	1	2	1	0	0	0	3	0	0
Monocytes	12	18	29	30	31	36	17	14	15	18	8	10	6	26
Lymphocytes	18	22	38	33	21	55	17	28	31	44	14	14	61	48
Plasma Cells	25	27	17	20	5	8	13	18	13	12	5	17	24	6
Large Primitive Cells	21	17	31	25	17	25	13	10	30	28	11	11	26	24
Small Unidentified Cells	28	16	43	56	33	44	37	41	45	61	22	12	32	24

TABLE 2.—PERIPHERAL BLOOD EOSINOPHILS AND MARROW CELLS BEFORE AND AFTER INTRAMUSCULAR ACTH

1. Patient	*M.F.P.*		*E.M.*		*G.C.*		*C.P.*		*T.P.*	
	Before ACTH	*After ACTH*	*Before ACTH*	*After ACTH*	*Before ACTH*	*After ACTH*	*Before ACTH*	*After ACTH*	*Before ACTH*	*After ACTH*
2. Blood Eosinophils/mm.^{3} by chamber count	1595	571	608	307	226	69	684	573	541	136
3. Marrow Cell Types/1000 cells counted:										
Myeloblasts	3	0	0	0	0	0	1	4	2	1
Promyelocytes	11	11	5	6	4	11	10	16	17	16
Myelocytes	103	130	51	75	122	85	66	91	79	68
Metamyelocytes	132	152	76	94	92	91	102	76	141	114
Neutrophils Band	185	183	190	168	73	113	106	104	171	153
Neutrophils Segmented	120	104	136	130	112	106	154	113	133	110
Eosinophil Myelocytes	29	38	12	15	6	7	14	15	50	61
Eosinophil Metamyelocytes	27	14	15	13	8	8	21	9	46	43
Eosinophils Band	23	30	26	15	9	9	20	17	25	23
Eosinophils Segmented	33	26	12	36	12	16	20	28	34	26
Basophils	1	1	7	5	2	2	2	2	2	7
Erythroblasts	3	3	2	7	5	11	11	2	4	4
Early Normoblasts	23	23	13	33	22	34	53	50	16	37
Intermediate Normoblasts	79	48	113	102	116	118	110	133	54	98
Late Normoblasts	82	88	198	178	298	194	177	203	128	96
Megakaryocytes	4	1	6	1	0	0	0	2	1	1
Monocytes	16	33	40	21	19	31	23	30	16	16
Lymphocytes	45	34	34	23	53	78	46	32	20	43
Plasma Cells	13	17	7	7	17	18	6	6	12	14
Large Primitive Cells	28	23	12	18	21	34	21	24	12	22
Small Unidentified Cells	40	41	45	53	9	34	37	43	37	47

either the sternum or iliac crest were done immediately before and 4 hours after the ACTH. Peripheral blood specimens were obtained just prior to the injection and at hourly intervals to a total of 5. In 7 patients the ACTH was given intravenously, 25 mg. in 1000 cc. of 5% glucose and water in a slow drip extending over an interval of 7 hours. Bone marrow aspirations were done just before and immediately following the infusion. Peripheral blood specimens were obtained before and at 2-hour intervals, as well as at the end. Differential counts of marrow cells were made on films stained with Wright's stain and 1000 cells counted before and after the administration of ACTH. Since we believe that accurate absolute cell counts cannot be obtained from aspirated marrow specimens (because of varying dilutions with blood) the marrow cells are reported as numbers of each cell type per 1000 cells counted. All marrows were cellular and the areas counted were selected to contain the least amount of dilution by peripheral blood. In addition to the chamber eosinophil determinations, routine differential counts on 200 peripheral blood cells were done, utilizing films stained with Wright's stain. The absolute number of each cell type was obtained by multiplying the percentage by the total white cell blood count.

TABLE 3.—PERIPHERAL BLOOD CELLS* PER MM³ BEFORE AND AFTER ACTH AVERAGES OF 12 PATIENTS

	Before ACTH		*After ACTH*		*Per Cent Change of Average*
	Average	*Range*	*Average*	*Range*	
Band Neutrophils	294	0–1680	530	0–2424	+32%
Segmented Neutrophils	4483	3143–7560	6175	3655–12,048	+27%
Eosinophils	565	77–1241	224	38–364	−60%
	596**	226–1595	187**	0–573	−69%**
Basophils	60	0–231	54	0–122	−11%
Monocytes	659	178–1289	454	198–1027	−31%
Lymphocytes	1395	351–2770	1008	365–2519	−28%

* All values except chamber eosinophil counts were derived from differential counts of blood films, and simultaneous total white cell determinations.
** Chamber counts. The percentage decrease in eosinophils after ACTH ranged from 100% to 16%. In only 2 patients was this less than a 50% decrease.

Results. Examination of the data (See tables 1-4) shows the expected decrease in peripheral blood eosinophils following ACTH. There was an average percentage decrease of 69% as determined by chamber counts on blood specimens obtained at the same time as the marrow specimens. The average percentage decrease as determined by differential counts of the stained blood films was 60%. There was a greater percentage decrease in blood eosinophils after the intravenous ACTH (83%) than after the intramuscular ACTH (55%). It was thought justifiable, however, to group the cases together. There was no consistent change in the marrow eosinophils immediately following ACTH; in fact, the total number before and after ACTH was remarkably constant. Furthermore, there was no significant change in the number of marrow eosinophils in their various stages of development, or evidence of degenerating forms. A comparison of the averages of the other marrow cells, before and after ACTH, likewise revealed little change.

Discussion. The present study was limited to the immediate effects of ACTH, and different results might be noted after prolonged administration. The fact that there was no significant change in the number of marrow eosinophils in their various stages of development suggests that there was no immediate interference with their rate of maturation. The possibility of destruction or of sequestration of the circulating eosinophils in some organ or tis-

sue remains. Evidence for the storage of eosinophils, temporarily at least, in the liver, spleen, or lymph nodes following the injection of adrenalin or cortisone is available in animals[1,2,4,7,10].

There are several reports of studies of the effects of ACTH and of cortisone upon the bone marrow in the human being. In most of these the intervals between initial administration of the drug and bone marrow aspiration are same after ACTH. Rosenthal and others[8,9], obtained similar evidence by following peripheral blood and bone marrow eosinophil counts on patients who had received cortisone or ACTH for a 2 to 12-day period. They found no change in the percentage of the eosinophilic cell count in the bone marrow in relation to the nucleated cells, and concluded that cortisone or ACTH increases the rate of removal of eosin-

TABLE 4.—BONE MARROW. CELLS PER 1,000 ± S.D.

Cell Type	*Mean Before ACTH*	*Mean After ACTH*	*Difference between means*	*Standard error of difference between means*
Myeloblasts	1.5 (± 1.3)	0.6 (± 0.5)	— .9	0.4
Promyelocytes	13.5 (± 7.8)	13.8 (± 4.9)	+ .3	2.7
Myelocytes	104 (±29.4)	108 (±46.0)	+ 4	15.8
Metamyelocytes	112 (±20.2)	105 (±25.6)	+ 7	9.4
Neutrophils Band	147 (±43.1)	141 (±37.2)	— 6	16.4
Neutrophils Segmented	123 (±23.6)	116 (±33.5)	— 7	11.8
Eosinophilic Myelocytes	17.3 (±11.7)	20.5 (±14.4)	+ 3.2	5.4
Eosinophilic Metamyelocytes	16.1 (±11.1)	16.8 (±11.1)	+ .7	4.6
Eosinophils Band	16.1 (± 7.5)	14.4 (± 7.8)	— 1.7	3.2
Eosinophils Segmented	20.4 (± 7.8)	19.5 (± 8.2)	— .9	3.3
Basophils	2.7 (± 2)	3.1 (± 1.7)	+ .4	0.8
Erythroblasts	5.8 (± 3.3)	6.9 (± 3.3)	+ 1.9	1.4
Early Normoblasts	30 (±17.3)	35.0 (±15.6)	+ 5	6.7
Intermediate Normoblasts	97.8 (±24.6)	106.7 (±31.3)	+ 8.9	11.5
Late Normoblasts	173 (±50.9)	159 (±37)	—14	16.2
Megakaryocytes	1.5 (± 1.4)	1.1 (± 1)	— .4	0.7
Monocytes	19 (± 9.5)	24 (± 8.1)	+ 5	3.6
Lymphocytes	33 (±15)	38 (±13.3)	+ 5	5.8
Plasma Cells	13.1 (± 6.6)	14.2 (± 6.2)	+ 1.1	2.7
Large Primitive Cells	20.3 (± 7)	22.6 (± 7.3)	+ 2.3	2.9
Small Unidentified Cells	34.0 (±10)	39.3 (±14.7)	+ 5.3	5.1

longer than those in the present study. Godlowski[6] showed that in man there was not any significant change in the number of eosinophils in the marrow following administration of insulin or adrenalin although there was a definite drop in those in the blood. He counted only mature and young eosinophils in the marrow and compared these with the number in the circulating blood. It has been shown that the eosinopenia produced by epinephrine may be independent of adrenal stimulation, hence, one cannot conclude from these studies that the effects would be the ophils from the blood without affecting their production by the bone marrow. On the other hand, the studies on the bone marrow and peripheral blood of patients with Hodgkin's disease treated with cortisone, by Straus *et al.*[11], showed an increase of both mature and immature marrow eosinophils on the seventh and fourteenth day of treatment.

The presence of an unchanged number of mature eosinophils in the marrow immediately after ACTH, coincident with the maximum depression of the blood eosinophils, as shown in our

cases, suggests that whatever the mechanism of removal may be, it is not associated with an early rapid mobilization of the eosinophils from the marrow. Thus, it is not comparable to the situation sometimes seen when an overwhelming infection calls out all available neutrophils and depletes the marrow of mature forms.

It seems unlikely that the blood eosinopenia can be explained by a cessation of maturation of marrow eosinophils associated with continued removal from the blood at a normal rate. If this were true, it would require a turnover of more than half of the eosinophils in the blood in less than 8 hours. The fact that normal appearing marrow eosinophils are present in all stages of development during early ACTH blood eosinopenia is against the concept of inhibition of maturation. Our data as presented here show no reciprocal relationship between the circulating and marrow eosinophils and no evidence of phagocytosed or degenerating eosinophils in the marrow. This is further evidence that the bone marrow is not the site wherein eosinophils are sequestered or held captive following ACTH.

Available evidence from animal and human experiments indicates then, that the bone marrow is not chiefly responsible for the eosinopenic response produced by ACTH, either through rapid inhibition of maturation of eosinophils or failure to release mature eosinophils into the circulating blood. Sequestration in some other reticulo-endothelial tissue is a more probable explanation for their rapid disappearance.

Summary. Studies of the blood and bone marrow showed that the immediate eosinopenic response to ACTH was not associated with morphologic evidence of disturbed maturation of the eosinophils. Neither was there evidence of depletion of mature forms by rapid removal or of destruction of the cells in the marrow.

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ACUTE NEPHROSIS:
THE KIDNEY OF ACUTE RENAL FAILURE

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THE kidney alterations responsible for the clinical phenomena of acute renal failure have been the subject of many studies and reports during the past decade. The pathogenesis of the condition remains obscure, or at best debatable. It is a disease of many aliases, and none of its currently popular names is entirely acceptable. Some, such as "lower nephron nephrosis"[25,106], and "acute tubular necrosis"[24] are inaccurately descriptive of the renal lesion. "Gestation nephrosis"[63], "hemoglobinuric nephrosis"[11] and "crush kidney"[27-35] have the disadvantage of being too restrictive, since all these conditions share morphological and functional characteristics. Other names, such as "renal anoxic syndrome"[111], "tubulovascular renal syndrome"[111], and "vasomotor nephrosis"[82] are unacceptable because they imply pathogenetic mechanisms not yet established, and whose role remains debatable. Other less familiar names are given in Zollinger's recent review[178], to which he adds the jarring expression "renal glaucoma" (Nierenglaukome).

It is proposed here that the condition is most suitably and accurately described by Minami's term "acute nephrosis"[121]. The constant, and probably basic, lesion in all cases of acute renal failure is a degenerative change in the epithelium of the renal tubules. For precisely such conditions the term nephrosis was originally introduced by F. Müller in 1905[124]. When used in this sense the term has both precision and brevity. "Acute nephrosis" has the further advantage of historical priority over most of the other names for the kidney of acute renal failure. The primary object of the present review is to outline the extent and character of the kidney lesions of acute renal failure and to indicate the principal concepts of their pathogenesis.

Historical Review. Renal damage associated with hemoglobinuria was de-

scribed during the 19th century by Ponfick[139] in cases of blackwater fever. In 1903, Plehn[138] ascribed the anuria of blackwater fever to nervous inhibition, but commented on focal epithelial loss in the nephrons as indicating a possible area of tubulovascular communication. Also in blackwater fever, de Haan[49] described dilatation of renal tubules, interstitial edema and infiltration, cloudy swelling and fragmentation of epithelium, and identified hemoglobin casts in convoluted tubules. De Haan attributed anuria to the combined effects of lowered filtration pressure consequent to blood pressure fall, and to tubule blockage by hemoglobin casts. Similar changes were noted by Werner[169] who referred also to therapeutic renal decapsulation. Experimental hemoglobinuric nephrosis was reported in 1911[172] in rabbits injected with hemoglobin solutions during hypotension.

Fatal renal damage resulting from crushing injury was reported by Hackradt in 1917[82], and later by Bredauer[22] and Minami[121]. These authors agreed in attributing the degeneration of renal tubules to toxic metabolites released from crushed musculature, acting either directly on tubule epithelium[121] or through the induction of vasoconstriction[22,82]. These early studies are of interest in that they anticipate many problems in pathogenesis which are still the subject of investigation and debate.

Clinical Background of Acute Nephrosis. Acute renal failure apparently may be reached by a variety of clinical pathways. Although the number of clinical states preceding renal damage is now very great, it is customary to group them into general classes sharing common features. Such simplification must of course recognize a broad overlap between groups. Phenomena such as prolonged shock and dehydration are common in all the groups of clinical states listed below, and may possibly be the pathogenetic link between them.

Kimmelstiel[93] collected, under the designation "acute hematogenous interstitial nephritis", cases of renal damage associated with infectious diseases, septicemia, blood transfusion and liver damage. Fishberg[66] expanded this group of etiological conditions to include blackwater fever, eclampsia, paroxysmal hemoglobinemia, and poisoning by potassium chlorate or mushrooms. This tendency to equate a single renal lesion with a variety of initiating factors[161] led to the description of the "disease" lower nephron nephrosis by Lucké in 1946[106]. The growing list of antecedent clinical phenomena was divided into 5 main groups in a review by Darmady[45]. These included renal failure following (1) shock, (2) disturbances of electrolyte and water balance, (3) disorders of pigment metabolism, (4) allergy, and (5) chemical nephrotoxins. A similar subdivision will be employed here.

BLOOD DESTRUCTION. Oliguria or anuria associated with degenerative changes in renal tubules and heme pigment accumulation have been reported frequently in blackwater fever, and following episodes of massive intravascular hemolysis[11,49,66,138,139,161,169]. Transfusion, usually with incompatible blood, has led to similar changes in many reported instances[5,17,42,48,50,53,68,74,123,148,161]. Sussman and Kayden[159] have reported finding both old and recent tubular damage in the kidneys of a patient with paroxysmal cold hemoglobinuria, but de Navasquez[50] was unable to demonstrate evidence of renal insufficiency in a similar case, even during aciduria. Tomb[161] refers to renal failure associated with pernicious anemia. In general, however, renal failure associated with blood destruction seems to occur mainly in cases where hemolysis is

both acute and massive, as in blackwater fever or in incompatible transfusion. Nevertheless, Foy *et al.*[68] were unable to relate the presence or absence of renal failure to the quantity of hemoglobin liberated in the circulating blood.

DEHYDRATION, SHOCK, AND ELECTROLYTE DISTURBANCES. Severe dehydration, shock and electrolyte disturbances may precede the onset in other cases of acute nephrosis. All these phenomena occur simultaneously or in sequence in the majority of cases, though in Bailey and Rubinstein's case of renal failure following cardiac arrest[7] shock would seem to be the dominant precipitating factor. Renal failure in cases of cholera cited by Tomb[161] appears in a background of grossly altered fluid and electrolyte metabolism, as well as shock. Dehydration and alkalosis[120,125,177] or acidosis[104] have preceded acute renal failure, though shock may also have participated. Similar renal damage has been seen in infants with severe diarrhea and acidosis[179], and in heat stroke[112]. Renal damage of this type has been produced experimentally in salt deficiency and dehydration[176], ammonium chloride acidosis[79] and by dehydration alone[100,101].

TISSUE DESTRUCTION. The wave of current interest in acute nephrosis began with the publication of reports by Bywaters and his collaborators on cases of acute renal failure following crushing injury sustained during air raids[10,27-35]. During and after the period of these reports, others of a similar nature appeared under a variety of titles: "syndrome of acute severe myolysis"[20], "pigment nephropathy"[156], "traumatic uremia"[46,132] and "crush injury"[75], while further cases were simply recorded as renal damage after crushing[14,161] or after prolonged burial[52]. Cases of the same type had been noted during and after World War I[22,82,121] without attracting much interest. It seems probable that improvements in treatment of the severely wounded increased the immediate survival rate among such cases during and after World War II, so that greater numbers of patients lived long enough for renal failure to become manifest[168]. The increased use of transfusion therapy must have added to the numbers of renal failure cases, although transfusion hemolysis cannot be blamed for them all. Several instances of renal failure following crushing trauma have been recorded in which transfusion was not employed[10,29,44,117].

The role of muscle damage (usually considered ischemic) is emphasized in reports of renal failure following non-traumatic muscle destruction[20,32,72]. Although Tomb[162] has argued against a toxic pathogenesis of kidney damage on the grounds that renal failure does not occur after infarction, a few such cases have now been reported. Paxson *et al.*[133] described renal failure associated with torsion and hemorrhage into an ovarian cyst. Pulmonary infarction[97] and Volkmann's ischemic contracture[75] have also preceded renal failure. In none of these cases, however, was tissue necrosis an isolated episode. In the two former, hemorrhage and hemolysis may have played some role, while in the latter there was severe brain injury with hyperthermia.

Renal failure has followed severe burns in children[62] and adults[76,108]. Other cases in childhood have been associated with operation and sulfonamide therapy[146]. Both these latter examples must also be considered as probable instances of dehydration, shock and electrolyte disturbance.

ACUTE NEPHROSIS IN PREGNANCY. Occasional episodes of acute renal failure related to pregnancy may show the lesions of acute nephrosis. Most cases in this class are seen in association with eclampsia[8,63], although Lucke[106] has drawn attention to the occurrence

of damage to kidney tubules and renal failure following retroplacental hemorrhage[133,173] and uterine rupture[133]. Bratton[21] reports fatal renal damage following septic abortion, and Humphrey and Jones[89] describe 4 cases of post-abortion oliguria and anuria which survived.

ACUTE NEPHROSIS IN POISONING. A wide variety of toxins is capable of producing uremia and destruction of renal epithelium. A partial list would include inorganic corrosives such as bichloride of mercury[106], and uranium salts[145,171], as well as a great many organic materials including chloroform[106], carbon tetrachloride[106,154], diethylene glycol[106] and poisonous mushrooms[164]. In most of these the renal lesions differ from those considered in the previous sections in that they tend to involve the nephron diffusely. There is often outspoken necrosis of tubules and the changes tend to be most pronounced in the proximal convoluted tubules. In spite of these differences of intensity and location, the clinical aspects together with morphological alterations, to be outlined below, justify their inclusion as examples of acute nephrosis.

Renal damage and failure following use of sulfonamide drugs often is associated with degenerative lesions of tubules[65,69,70,81,107,142]. Many cases of this type might justifiably be considered in Darmady's allergic group, since the dose of sulfonamide is often very small[142], or the patient shows other evidence of allergy such as asthma[65].

The foregoing survey of the varied clinical background of acute nephrosis cannot be complete within the scope of this paper. Darmady's allergic background[45] has been omitted, without intending to deny its possible importance, but merely because it is extremely difficult to establish in individual cases.

The clinical features in all groups are similar, with expected variations in duration and intensity. The pathological changes in the kidney are, with the exception of certain poisonings, sufficiently similar from one group to the next to justify the belief that we are dealing with a single morphological endpoint reached from different beginnings, and possibly by diverse pathways.

Clinical Features of Acute Nephrosis. A detailed survey of clinical findings in acute nephrosis is beyond the scope of this communication. Recent comprehensive reviews have given exhaustive coverage of this aspect of the condition[160,178]. After the clinical phenomena of the initiating injury or disease, the cardinal features of acute nephrosis become manifest within 24 hours. Urinary output falls precipitously[178] and complete anuria may appear within the first day. Death when it occurs during the first day or two is usually ascribable to the precipitating condition. If anuria persists, there is a rapid rise in blood concentration of nitrogenous wastes (urea, creatinine, non-protein nitrogen, uric acid). The rise in non-protein nitrogen in the blood is steepest during the first 4 or 5 days, but uremic levels may persist in surviving patients even after urinary output has been restored[141].

Such urine as is produced is of low specific gravity. Recovery of urine production, when it occurs, is usually between the 5th and 10th day from the onset of oliguria. The possibility of later restoration of renal excretory function is precluded in other cases by death in uremia. During this recovery period, 24-hour-urine output may be as high as 4 or 5 liters a day or more, but the product continues to be of low specific gravity. Dilute polyuria may continue for a week before slowly subsiding toward normal.

As early as on the third day of anuria, elevation of blood pressure may be noted. Both systolic and diastolic pres-

sures are high, and truly hypertensive levels are common. Blood pressures of the order of 300/200 mm. Hg have been recorded[178]. Disorders of blood electrolyte concentration may be seen throughout the course of the disease. Early, when there has been intravascular hemolysis or tissue destruction, high serum potassium levels may be noted[88]. During the oliguric phase sodium and chloride concentrations in the serum may be depressed[91]. High serum potassium values have also been noted toward the end of the first week[91]. During the polyuric phase of incipient recovery, there may be evidence of impaired electrolyte homeostasis during which lack of careful control of therapy may lead easily to either hypo- or hyper-natremia, and hypokalemia[91,141]. With recovery there is a gradual fall of blood pressure to preexisting levels and a slow, often protracted return of the urine to normal quantity and concentration.

Pathological Changes in Acute Nephrosis. Any reviewer of the subject of acute renal failure cannot help but be impressed by two things. First, there is widespread disagreement, bordering at times on acrimony, amongst morphologists concerning the nature and distribution of the renal lesions. Secondly, and to some extent because of this anatomical confusion, there are a great many opinions about nearly all aspects of the pathogenesis of the lesions and of the renal functional impairment.

At least some of the disagreement concerning the lesions themselves can be ascribed to the fact that different investigators see cases of different duration and varying clinical backgrounds. Concerning microscopic morphology, some appear to consider as artefactual post-mortem autolysis what others interpret as significant degenerative lesions. This seems particularly true in the case of changes in the proximal convoluted tubule epithelium where autolysis may develop with varying speed and intensity. Furthermore, before accepting a particular observation of alteration in a specific segment of the nephron, it must be recognized that the greater the degree of damage to the tubule, the less is the certainty with which this segment of the nephron can be identified in ordinary sections. The studies of Oliver *et al.*[128] wherein individual nephrons were dissected out for study, make it clear that such misinterpretations have been common. Even micro-dissection studies, while unsurpassable for the identification of the location of more striking foci of nephronal damage, must suffer from the disadvantages inherent in the use of the strong solutions the technique requires. It is doubtful whether finer degrees of cytological alteration can be accurately observed by this method.

It is perhaps well to remind ourselves that pathologists are merely witnesses to biological accidents. Even those who observe the same catastrophe may be impressed by different features of it, and may give correspondingly divergent testimony.

GROSS APPEARANCE. Most observers agree that the gross appearance of the kidney in acute nephrosis is lacking in diagnostic features[27-35,44-46,106,178]. Both kidneys are usually uniformly enlarged to a moderate degree. The external surface may be purplish with vascular engorgement, but often of normal color. The organ is moderately firm, or of normal consistency. There is commonly some bulging of the cut surface and the distinction between cortex and medulla may be exaggerated by hyperemia of the latter. Cortical striations may be emphasized by hyperemia or partly obscured and glistening when edema is marked.

MICROSCOPIC APPEARANCE. The glomeruli rarely show striking alteration. Dilatation of Bowman's space has been noted in cases of transfusion anuria[17].

After crushing trauma, accumulation of loose protein precipitate has been noted frequently[31,56,77,173] in the space. The epithelium of Bowman's capsule may show hypertrophic thickening[31,113], but this is inconstant and has not been seen by some observers[178]. Glomerular ischemia has been described in transfusion[50], blackwater fever[110], and traumatic anurias[77], as well as after uteroplacental damage[173]. Goormaghtigh[77] has described heavy granulation of the afibrillar cells of the afferent arteriole portion of the juxta-glomerular apparatus, as well as occasional vacuolation of the cytoplasm of these cells. He implies liberation of a vasopressor substance which produces arterial spasm at the vascular pole of the glomerulus. In general, however, it may be said that glomerular changes are of minor degree, and indeed have not been noted at all in many reports.

Alterations in the renal tubules, on the other hand, have been described by all observers to whom histological material has been available. In many reports, particularly in the earlier ones, little information is given as to the location of these lesions in proximal or distal convoluted tubules, Henle's loops or collecting tubules. De Haan in 1905[49] noted tubule dilatation in blackwater fever patients and this was confirmed a short time later[169]. Similar dilatation also has been seen in traumatic[113], transfusion[17] and other[66] acute uremias.

Degenerative changes of varying intensity in the epithelium of the tubules have been noted in all reports. These alterations have varied from minor degenerative changes[21,121] or vacuolation[30] to degeneration and necrosis[17,48,49,66,90,120] as well as evidence of regeneration[17,120] or even rupture of the affected tubule[70]. Thrombosis in small vessels (usually veins) has been seen frequently in relation to damaged tubules[5,31,56,106,107,120]. Such thrombi may be small mural deposits which do not occlude the vessel[5]. This change apparently can progress to rupture[138] and "tubulo-venous aneurysm" formation in some instances[44,178], or to herniation of the damaged tubule into the vein[32]. The latter event might indicate higher pressure in the tubule than in the vessel at the time of herniation.

The changes in the tubules mentioned above have usually been the subject of general description, rather than being referred to specific segments of the nephron; but where landmarks have been noted, cortical position of the affected tubules is usually indicated. In publications where the architecture of the nephron is specifically considered, most authors have described changes in the proximal convoluted tubules, but have found these less marked than those lower down the nephron.

The most striking damage in the proximal tubule has been seen in poisonings of various types, where epithelial necrosis is common[59,73,98,109,119,126], and usually more pronounced than elsewhere in the nephron. In other cases proximal tubule damage has been noted as "catarrhal changes"[44,79], slight dilatation with cloudy swelling[5,106], atrophy and dilatation[113], or vacuolation of epithelium with occasional hyalin droplet formation[178]. Few observers have noted casts in the proximal tubules, although Bywaters and Dible[31] found plugs of apparent cellular debris in some of their traumatic cases. The micro-dissection studies of Oliver *et al.*[128] have shown that epithelial degeneration, tubule rupture and cast precipitation may be seen in localized segments of proximal tubules, though they are less common here than lower down.

Mallory[113] was of the opinion that some of the dilatation seen in proximal tubules was artefactual, due to shrinkage during preparation of sections, but

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felt that even when artefact could be discounted, appreciable dilatation was present. This is in agreement with later observations[178] in which maximal dilatation was found between the 7th and 9th days after the onset of renal failure. It is perhaps worth noting that the proximal tubule alterations referred to above can scarcely be ignored, since they have been described by numerous competent morphologists who must be accustomed to discounting changes of shrinkage and autolysis. Indeed, some of the authors referred to[178] assign no significant pathogenetic role to the tubule changes they describe.

Among those who have studied Henle's loops in acute renal failure there is agreement that some alteration is usually present[31,44,48,66,74,113,178], although Lucké[106] and French[70] found changes mainly confined to the thick limb of the loop. Bywaters and Dible[31] found foci of epithelial necrosis in the vicinity of junction between Henle's loop and the distal convoluted tubule, usually in the neighborhood of large veins. Hyalin casts, but no pigment deposits, were occasionally present, and some of these damaged tubules appeared to herniate into the lumina of veins. Interstitial edema and cellular infiltration were common in the vicinity of damaged tubules. Similar damage has been described by Darmady[14]. Others[48,66] have noted pigment casts in the loops.

There is general agreement that more or less striking lesions are to be found in the distal convoluted tubules in most cases[5,31,44,48,56,75,76,106-108,120,173,178,179]. These vary from changes of cloudy swelling to necrosis and rupture of tubules. It has been pointed out repeatedly that the changes tend to be localized within the affected segment, or at least to vary in intensity from one area to another[3,5,56,106]. The focal character of the tubule lesions does not appear to have attracted much interest until it was so strikingly illustrated in the nephron dissections of Oliver *et al.*[128]. Their report clearly showed that focal degenerative or disruptive lesions may occur at any point in the length of the nephron or collecting tubule system, and, though often associated with cast precipitation, may occur in its absence. The localized nature of these pronounced changes makes it apparent that in the ordinary microscopic section little alteration may be seen, because every nephron in it might have its foci of damage outside the plane of section.

Granular pigment casts derived from either hemoglobin or myoglobin[106] are commonly seen in the distal tubules and are usually associated with necrobiotic changes in the epithelium. In a case of renal failure in eclampsia, Fahr[63] noted unusual epithelial proliferation in relation to casts which became engulfed and no longer lay in the lumen of the tubule.

Pigment casts are also common in the collecting tubules[17,31,66,113]. Ayer and Gauld[5] have described epithelial necrosis and accumulation of heme pigment in the cytoplasm of tubule lining cells, as had been noted earlier by Bordley[17]. Mallory[113] found degenerative changes in the epithelium of collecting tubules only in relation to casts.

Regenerative activity has been noted in tubule epithelium from about the fifth day onwards[178] and is usually most marked in the distal convoluted tubules and collecting tubules where the newly grown epithelium is sometimes thrown into folds or plications[31].

Abnormalities of interstitial tissue and vessels have been described in many reports and given varying emphasis[5,17,21,31,63,70,74,93,135,178,179]. Edema and cellular infiltration were described by Bordley[17] and by other early workers[48,63,74]. Kimmelstiel[93] described both focal and diffuse cellular exuda-

tion of plasma cells, lymphocytes, eosinophils, monocytes and polymorphonuclear leukocytes. Mallory[113] and others[5] observed interstitial granulomas in relation to damaged tubules containing casts. Bywaters and Dible[31] found no significant interstitial edema until at least 5 days after crushing injury, an observation which agrees with that of Zollinger[178]. The latter found edema most marked in the medulla, less so in the cortex, and least of all in the renal papillae. He noted that the edema and cellular exudate tend to be focal in the cortex, confined to the vicinity of blood vessels, which in some cases appear narrowed.

The occurrence of venous thrombi in relation to damaged tubules, with or without tubulo-venous rupture[45] or herniation[31] has already been referred to. In addition, Goormaghtigh[77] has noted intimal granulomas in interlobular veins. He also made the observation that the intertubular capillaries contain blood, although Mallory[113] found cortical blood vessels collapsed.

In resumé, it is apparent that any portion of the nephron from the glomerulus down to and including the collecting tubules may show alteration in acute renal failure. In areas of damage, changes in the epithelium of the tubules are primarily degenerative in character and may progress to necrosis and tubule disruption. Lesions tend to be most evident in the lower portion of the nephron, where pigment casts are common. The tendency for tubule lesions to be localized to knuckles of the tubule between less damaged segments may make the amount of damage appear slight in microscopical sections in view of the apparent total suppression of renal function. While changes in the tubules are insignificant in early cases, interstitial alterations are not detectable at all until after at least 3 or 4 days of renal failure. It is the reviewer's opinion that the most constant morphological alteration in all cases is that of degeneration of tubule epithelium. This is the lesion by which the condition is most readily recognized in microscopic sections. If, as has been proposed[93,178], the interstitial alterations are fundamental, many early cases must be undiagnosable on this basis. It seems wisest at the present to call the condition by a name that implies its most constant morphology, and which leaves the way open for further exploration of its pathogenesis. The term "lower nephron nephrosis" must be rejected in spite of its appeal to the tongue, since it is clear that the lesions are not by any means so narrowly confined as the name implies. Indeed, the only suitable name based on the morphology of a condition of acute tubular degeneration appears to be that of "acute nephrosis."

Etiology and Pathogenesis. Almost every conceivable mechanism has been suggested for the development of the lesions of acute nephrosis and for the accompanying oliguria and anuria. Early theories postulated toxic damage to tubular elements. This was a logical development, since the truly toxic nephroses were among the earliest degenerative lesions of renal tubules recognized. Hypotheses implicating nephrotoxic materials are still the basis of much investigation. Among these concepts those which have attracted the greatest interest are those dependent upon the effects on the kidney of pigments derived from red blood cells and from striated muscle.

The second main group of hypotheses may be collectively designated as concepts of primary circulatory disturbance, in which shock, vasospasm, reduced renal circulation and local anoxia are considered fundamental. A smaller group of investigators has been more impressed with the interstitial reaction in the kidney and considers

the basic lesion one of inflammation and exudation. Various concepts, of course, attempt to implicate the foregoing theories in concert or sequence and may be classed as combination theories.

In any evaluation of pathogenetic concepts it is necessary to realize that some hypotheses are aimed primarily at explaining the development of the lesions, whilst others are more concerned with elucidating the mechanism of oliguria and anuria. Superficially these two approaches may seem identical, but they differ in the tendency of the morphologist to offer explanations only on the basis of observable structural change, while the physiologist is inclined to base his conclusions on the results of tests of function, regardless of visible changes in structure. Thus from the morphological standpoint we find anuria explained as a result of tubule blockage by casts, inspissated fluid, or elevated intrarenal pressure caused by edema, while physiologists are inclined to place more emphasis on changes in glomerular filtration rates or alterations in the resorptive activity of the tubules.

NEPHROTOXINS. One of the earliest explanations for the urinary pigment in blackwater fever was that hemoglobin was released by red blood cell destruction occurring in the kidney[138]. It was assumed that blood escaped via tubulovascular communications into the tubule fluid which had the capacity to induce hemolysis. Somewhat later, Bredauer[22] suggested that in renal failure due to trauma, toxic metabolites released from damaged muscle, induced hemolysis, although he attributed renal failure to intrarenal vasoconstriction. The effects of hemoglobin and myoglobin on renal structure and function have now been widely investigated. These studies have yielded valuable information about renal function, but leave considerable doubt concerning the pathogenetic role of pigments in acute nephrosis.

The demonstration by Baker and Dodds[9] that hemoglobin precipitated more easily at a pH below 6 and salt concentration over 1% led to the assumption that there was less danger of intratubular precipitation and consequent obstruction if the urine could be kept alkaline during bouts of hemolysis[64]. Experimental renal failure has been produced in rabbits with aciduria[99] or dehydration[36,39,102], or both[34] following intravenous injection of hemoglobin[99,102] or myoglobin[34]. Hemoglobin injection plus dehydration alone has also led to lesions of renal tubules and anuria[100], although changes have been found more severe when hypotension had been induced first[34,87, 101,172]. In dogs renal damage has resulted from hemoglobin injection, regardless of whether the urine was acid or alkaline[36,67]. Bradley[19] considered hemoglobin release together with acidosis to be of importance in causation of renal damage. In one experiment[67], in order to induce impairment of renal function, it was necessary to attain higher blood hemoglobin levels than are met with in humans following intravascular hemolysis. It should be noted that the rabbit normally excretes an alkaline urine, and Smith[155] has emphasized that in some of the experiments using this animal[34] the effects of the ammonium chloride used to induce aciduria have not been controlled. Others have considered the rabbit an unsatisfactory animal for experiments of this type because of its great vasomotor instability[23]. The failure of experiments attempting to induce renal damage in dogs by myoglobin injection[36] may in part be related to the much greater clearance rate for this material than that for hemoglobin[175].

Numerous experiments in which blood or muscle pigment have been injected into man or animals have fail-

ed to produce either clinical or morphological evidence of renal damage[131, 176]. Thus, Yuile *et al.*[176] were unable to demonstrate nephrotoxic activity of hemoglobin in rabbits with either acid or alkaline urine, but found that renal failure ensued when hemoglobin injection was preceded by a period of renal ischemia or by renal damage induced by sodium tartrate. Foy *et al.*[68] concluded that the induction of renal failure in man could not be related to blood hemoglobin levels during hemolysis, although the reverse has been found in experiments with dogs[67]. In a case of paroxysmal hemoglobinuria in man, de Navasquez[50] found no evidence of renal functional impairment during periods when the urine was acid. Others have failed to find hemoglobin or myoglobin nephrotoxic in experimental animals[3,13,54,63,174] and some have found hemoglobin more soluble in acid than in alkaline urine[50, 68]. This last observation is in agreement with the finding that solids are more easily excreted by the human kidney in an acid urine[177]. Other effects of hemoglobin which may have some bearing on the pathogenesis of renal failure are its vasoconstrictor[116] and, presumably related, pressor effects[2].

The above observations on the renal effects of blood and tissue pigments are not necessarily in disagreement. When surveyed together they suggest that the pigments in themselves have little damaging effect upon the kidney, but that together with hypotension (and by inference, lowered filtration rate), dehydration (and possible electrolyte disturbance) or simultaneous renal damage from other causes, they may in some way induce renal failure. The suggestion that pigments may exert a direct toxic action on the epithelium of the tubule would have to be interpreted in the light of these observations.

The possibility that potassium excess resulting from blood or tissue destruction might be nephrotoxic has been suggested a number of times[14,27, 88,89], but experimental investigation of this aspect is lacking. In view of the frequent occurrence of renal failure in states of dehydration and electrolyte disturbance, experimental study along these lines might yield valuable information.

Only one group of investigators appears to have been impressed with the possibility that breakdown of blood proteins might yield nephrotoxic materials[136]. In experiments with dogs, cats and rabbits it was found that the nephrotoxic action of erythrocytes appeared proportional to their protein content. It has been suggested that increased production of urea after trauma might be toxic to the anoxic kidney of shock[132]. Dunn *et al.*[56] considered it possible that excess uric and phosphoric acids resulting from tissue damage might have a toxic effect upon the kidney. At about this time McFarlane[118] reported lesions in the distal tubules in rats to which sodium acid phosphate was administered. Similar lesions had been described earlier in rabbits subjected to lithium monourate injections[58].

Efforts to demonstrate humoral nephrotoxic agents in the blood of traumatized animals have not had great success. Eggleton[60,61], however, found evidence of such material in the blood of crushed cats, and concluded he was dealing with an anaerobically produced intermediate muscle breakdown product. Goormaghtigh[77] has postulated the existence of a humoral vasopressor agent liberated during crushing injury. Some workers have identified the shock inducing agent and possible nephrotoxin as adenosine triphosphate released from damaged muscle[12,80,157], while others have referred merely to toxic metabolites derived from tissue

destruction[96,121,173]. The experimental production of renal tubule damage by repeated histamine injection does not appear to have been pursued further[85]. Mirsky and Freis[122] described renal lesions similar to those of crush syndrome in rabbits and rats injected with crude trypsin.

Myoglobin solutions injected into normal rabbits have failed to induce renal lesions or failure[34] but did so when the animals were submitted to crushing trauma and rendered aciduric. Similar results have been obtained in rats[38,39].

The significance of these experimental studies is difficult to evaluate. The idea of a nephrotoxic material released as a result of blood or tissue destruction may have been seized too eagerly. It may be that because known toxins such as bichloride of mercury produce necrosis of tubules, the occurrence of this lesion in other cases *ought* to be due to the action of some unidentified toxin. The search for such toxin has been a thorough one, but thus far the results suggest only that in the severely insulted organism some several materials may help in the induction of renal damage.

If in fact a nephrotoxic material is responsible for the lesions of acute nephrosis, it clearly must act in a different manner from other toxins. The latter produce tubule lesions in areas which can be related to tubule function, for example, the proximal tubule necrosis in bichloride of mercury poisoning. On the other hand, the lesions in acute nephrosis are haphazardly distributed up and down the nephron, showing variations in intensity which cannot be related to areas of functional specialization. Thus, while it cannot be denied that toxic materials may have an important role in the pathogenesis of acute nephrosis, the inference to be drawn from published reports is that toxins are either of subsidiary importance, or else that they act on the kidney indirectly.

VASCULAR DISTURBANCES. One such indirect pathway to renal damage which has aroused considerable interest in recent years is the whole complex of renal hemodynamics, including vasospastic phenomena, glomerular filtration and tubular reabsorption. A considerable number of investigators have reached the conclusion that reduction of renal blood flow is of primary importance in the pathogenesis of acute renal failure[16,44,46,68,77,87,104,111,130,134,137,140,152,153,154,156], although opinions vary as to how this local anoxia is produced, and how it operates to bring about renal failure.

Investigation of normal renal circulation has indicated that renal blood flow may vary independently from changes in the general circulation[149,166], and that the kidney does not compensate for diminished blood flow by increased oxygen extraction from the blood[166]. It is also apparent that there may be rather prolonged reduction in renal blood flow during shock, as a result of intrarenal vasoconstriction[165]. This has been found to result in reduced glomerular filtration[26,144,159], as had been guessed by de Haan[49]. There may also be an effect on glomerular permeability, which apparently is limited for hemoglobin[18,71]. There is probably a simultaneous lowering of oxygen supply to the tubules during reduced renal blood flow[68]. It is unreasonable to accept the suggestion that this should produce damage first in Henle's loops merely because they are the furthest point along the line of blood supply[6] since this makes the unjustified assumption of equal nutrient requirement in all parts of the nephron. Reduction of renal blood flow has been observed in experimental shock induced by limb tourniquets[40], burns[92], and by massive hemorrhage[15,37,92,137]. In similar experiments tempo-

rary anuria was observed during the period of hypotension brought about by hemorrhage[153] or trauma[129]. Axelrod and Pitts[4] have found, however, that moderate to severe hypoxia has no measurable effect on tubule function. By the more direct, but less physiological approach of inducing renal ischemia by clamping the renal artery, death from uremia resulted when the clamp was left in place for more than 2 hours in dogs[83], rats[94,95] and rabbits[6]. It has also been found that in rats urèmia is more easily produced by clamping the renal vein than by constricting the entire pedicle[150]. Experiments of this same type in dogs have indicated that after renal artery constriction there is an increase of capillary permeability within the kidney[158].

Several mechanisms by which reduction in renal blood flow might be brought about in shock have been suggested[77,87,105,116,130,147,163]. An early concept was that subthalamic irritation by protein breakdown products released during hemolysis led to general vasoconstriction in which that in the kidney was of prime importance[87]. Perfusion experiments have demonstrated a vasoconstrictor material in the blood of animals shocked in various ways[130]. Cross transfusion in dogs, however, failed to demonstrate antidiuretic factors in the blood of shocked animals[105]. Direct renal vasoconstrictor action has also been attributed to hemoglobin[116] as well as to the debris of laked red blood cells[147]. The hypothesis of an intrarenal shunt mechanism whereby cortical ischemia might be induced through vascular bypasses[163] has not been confirmed in other experiments[114,151].

Thus far, it may be said that renal failure does not appear to have been produced by experimental shock without renal artery constriction. The latter type of experiment cannot, on the data now available, offer a reasonable explanation for acute renal failure in man, since it clearly induces a degree of renal anoxia which would be incompatible with life if brought about by shock. Whether species difference makes the human kidney more susceptible to anoxic damage or local vasospasm is not clear. It has been suggested[178] that it may be easier to induce renal anoxic damage in large than in small animals.

THE MECHANISM OF ANURIA. Since the pathogenesis of the lesions of acute nephrosis remains somewhat obscure, there can be as yet no entirely satisfactory explanation of the mechanism of oliguria and anuria. Among the theories proposed the majority favor an intra-renal cause, though there are those who consider the uremia to be at least partly extra-renal in origin. Of the intra-renal causes suggested, the principal concepts are those dealing with obstruction of tubules by casts, intra-renal compression by edema, reduction in renal blood flow, and back diffusion of filtrate through damaged renal epithelium.

A number of investigators have held casts in the renal tubules primarily responsible for reduced or abolished urine production[1,9,49,55,65,114,127,167]. Indeed, it is clear that fluid cannot flow through blocked tubes and when casts are present, they must at least contribute to anuria. There are serious objections, however, to accepting tubule obstruction as the sole cause for anuria[11,20,31,35,47,48,50]. In many cases casts are too few to reasonably explain total suppression of urine[5,11,35,50], even though dilatation of the proximal nephron[5,106,113] might be taken to imply obstruction lower down. An alternative suggestion has been that increased viscosity of tubule fluid[84], or inadequate flushing of the nephron[68] might impede or abolish urine output. Some have considered casts to be the

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result of tubule damage rather than its cause[29,68,173], or have held that precipitates in the tubule lumen aggravate epithelial damage due to other causes[174].

It seems obvious that reduction of glomerular filtration from whatever cause[155] must contribute to oliguria. This is possibly enhanced by increased reabsorption from the tubules[51,57,58,115,143,154,165]. Increased tubule permeability has been found in experimental uranium[145,171] and oxalate poisoning[78,86], and the impaired electrolyte homeostasis in humans during recovery from anuria might well have a similar basis[91,141].

It is possible that uremia of acute renal failure may be increased by extrarenal factors such as dehydration and sweating[29,49]. Experimentally, sodium chloride deficiency has been found to produce lowered glomerular filtration, oliguria and elevation of blood urea concentration[103,170].

An important role in the pathogenesis of anuria has been attributed[41,135,178] to increased interstitial pressure caused by edema and inflammatory infiltration. Zollinger[178] conceives two phases of anuria, the first resulting from shock and reduced filtration rate, the second being due to increased intra-renal pressure. Such an explanation, however, suggests that with increasing edema there should be compression of veins and collapse of tubules, both of which are usually absent or insignificant. It is also difficult to see why the edema seen in kidneys of acute nephrosis should cause total anuria, when the more marked turgidity seen in bilateral acute pyelonephritis so rarely does so.

It is apparent that several features of the renal lesions may contribute to oliguria and anuria. Reduction in blood flow and filtration rate must play a role, at least during the period of shock. Obstruction of tubules may also contribute, and possibly throw an extra excretory load on unobstructed nephrons. Degenerated and necrotic tubule epithelium can hardly continue its normal selective functions and back diffusion of some degree seems reasonable in most cases. It is even possible that such diffusion when excessive might bring about the interstitial edema so common in late cases. Further renal damage and increasing uremia may well result from increasing breakdown of tissue and blood proteins, some of which may prove toxic to the already embarrassed kidneys.

At the present it may be said that we do not yet know with certainty how the lesions of acute nephrosis are produced, nor have we a clear understanding of the mechanism by which anuria results. The patient who develops acute renal failure is clearly in a state of extremely complex physiological derangement. It is difficult (or perhaps impossible) to reproduce this state exactly in experimental animals, whose metabolic adjustments may be made in quite different ways from those of the human. It is nevertheless to be hoped that the collection of further information on human subjects suffering from this condition, and the controlled experimental study of all aspects of renal structure and function in similar states may provide the data required to clarify some of the problems of acute renal failure that still remain obscure.

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EPIDEMIOLOGIC INFERENCES DERIVED FROM MATERNAL AGE

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THE elementary epidemiological characteristics associated with time, place and person[55] are the start of any analysis of mass disease in man. Secular trends, geographical distribution and seasonal variations in logical sequence call for consideration of the age, sex and race of the persons affected. Many clinical entities are associated with specific patterns in these data. The interpretation of the patterns themselves is not always clear, and is by no means uniform. All are open to further analysis; and profitably, in extending knowledge of the behavior of disease in populations of people. Age of mother at the time people are born and birth order in the family are two independent variables suggestively contributing to a more precise definition of those factors of age which contribute to disease. The information would seem to serve at least three useful purposes:

A primary clinical benefit is to aid prognosis for the individual patient. The clinician needs to know the risks of childbirth at various maternal ages as they affect both mother and child, for proper allocation of hospital beds, for determining the need for consultant services, and for guidance in drawing upon other facilities of modern medical care.

The demonstration of abnormally high risk attached to a particular age is a direct indication for preventive action. Such educational and administrative measures as may be applied on the single basis of that information are of course provisional, and await identification of the factors immediately responsible for the association of age and high risk. Insofar as such factors are separable from age, a more direct attack becomes possible.

Recognition of associations of age with specific maternal and fetal diseases or defects aids research in etiology of such conditions. The main emphasis on these two variables of late has been in relation to congenital abnormalities or to conditions closely associated with pregnancy and parturi

tion. Recent experimental work[104,173] suggests an influence that extends well beyond these limits, even to such unlikely fields as cancer.

The present purpose is to draw attention to rather widely scattered evidence linking various diseases, defects and biological characteristics with maternal age, and to consider possible interpretations of the observed associations. The ultimate aim is to examine demonstrated associations with maternal age, in an attempt to identify more direct relationships. In other instances, the principal concern is with the kinds of new evidence needed to establish the basic relation with age. By viewing the problem biologically rather than clinically, final attempt is made to identify associations theoretically probable, but thus far not explored, despite evident suggestion of a clinical and public health significance.

The first step toward the stated objectives is briefly to describe available methods for testing association between maternal age and a particular morbid state or physiological attribute. Two general methods are available, one indirect and one direct, and both are applicable to either maternal or infant characteristics. For maternal disorders the direct method of estimating incidence from known numbers at risk in the various age groups is more satisfactory, and is in fact the easiest way with the data usually available.

The first general method, usually ascribed to Greenwood and Yule[60] but originating in the "Short Table" of Pearson[144a,b], relies on a comparison of index cases with their siblings. The assumption is implicit that in the absence of an association with birth order or maternal age, the chances are random of a patient appearing at any of the maternal ages or birth ranks of the sibship. The method was originally used to determine the influence of birth order, but subsequently, as modified by Penrose[146d], was applied to consideration of maternal age and even for separation of the effects of birth order and maternal age. A method described by Haldane and Smith[67] rests on similar assumptions. An essential feature of these methods is that the families under consideration must be complete, a limitation that clearly affects their usefulness. Other difficulties relate to accuracy. Their main value is in first drawing attention to an association where data are limited.

The second group of methods depends on comparing birth ranks or maternal ages of patients with those of the general population from which the sample is drawn. Knowledge of the general population may be complete, as in the work of Yerushalmy[200a] on stillbirths and neonatal deaths; or may be obtained by sampling, as practiced by Record and McKeown[151a,b] in a study of malformations of the central nervous system. A satisfactory method of using data of vital statistics to estimate the maternal age distribution of the general population at the time of birth of a series of patients of various ages, has been described and used by Beall and Stanton[8a,b] in studies of epilepsy and mongolism.

Demonstration of an association between a specified characteristic or pathologic condition and maternal age raises the question of a closer association with some other variable closely linked with maternal age; for example, paternal age, birth order or parental fertility. Either of the two methods described serves in probing the question, at least for birth order and maternal age. The second requires less involved statistical method and is preferable, provided the necessary data are available.

Under circumstances where the association with maternal age is secondary to a relationship with some other quality, birth order for instance,

an erroneous interpretation is sometimes made that there is no association with maternal age. The association with maternal age is of course no less real because it happens to be indirect. The practical difference is that demonstration of a secondary association has been in the one situation successful, while in the other no closer association

lation and causation is a pitfall likely to be overlooked when examining associations, but no more so for maternal age than for many other biological characteristics.

The Maternal Risk. Variation in the risk of childbirth according to age of mothers may be measured satisfactorily, so far as mortality is concerned,

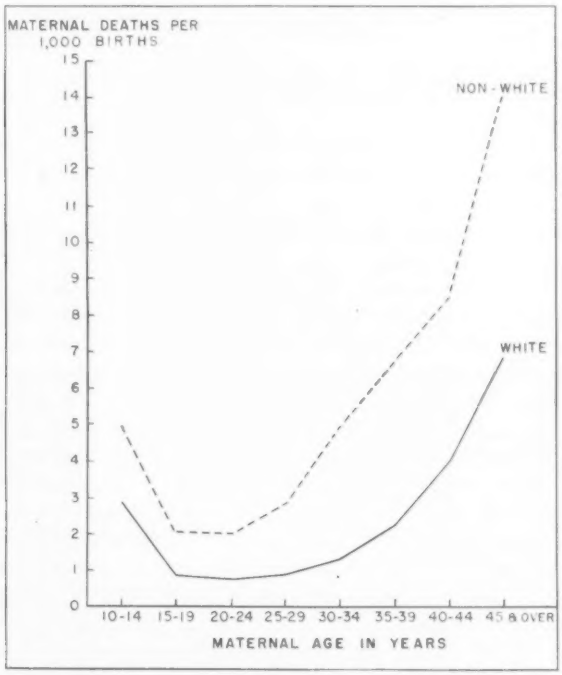

Fig. 1.—Maternal mortality rates per 1,000 total births by age and race, United States of America, 1945-1949.

than that with maternal age has yet been accomplished. Maternal age as such, "the mere accumulation of years"[82c], can hardly be considered a factor influencing disease. The issue is with conditions that attend advancing years. The more that knowledge improves, the more will characteristics now thought to be associated with age be relegated to the "no association" group. The distinction between correlation and causation is a pitfall likely to be overlooked when examining associations, but no more so for maternal age than for many other biological characteristics.

by officially reported data of offices of vital statistics. For morbidity, as well as for the separation of age effects from those of parity, reliance is necessarily placed on selected and special studies in clinics, hospitals, and sometimes for whole populations within the area of a town, county or other jurisdiction of practicable size.

MORTALITY. Age specific maternal mortality rates for the United States,

1945 to 1949, are presented in Fig. 1, with separate consideration of white and non-white populations. The essential inferences from the data are: (1) rates are lowest for both races in the age period 15 to 24 years; (2) for mothers under 15 years of age the rates are materially greater; (3) after age 25 years for non-whites, and 35 years for whites, mortality rates increase markedly with age. At ages 45 and over the rate for non-white mothers is 14.1 per thousand, more than 10 times the average rate for the child-bearing population; and (4) rates are higher at all ages for non-whites than for whites, but the general relationship between mortality for white and non-white does not vary greatly with age. Observations (2) and (3) may be extended to advantage by examining disease specific death rates for the three main causes of maternal mortality, as given by the U. S. Bureau of the Census, and illustrated in Fig. 2.

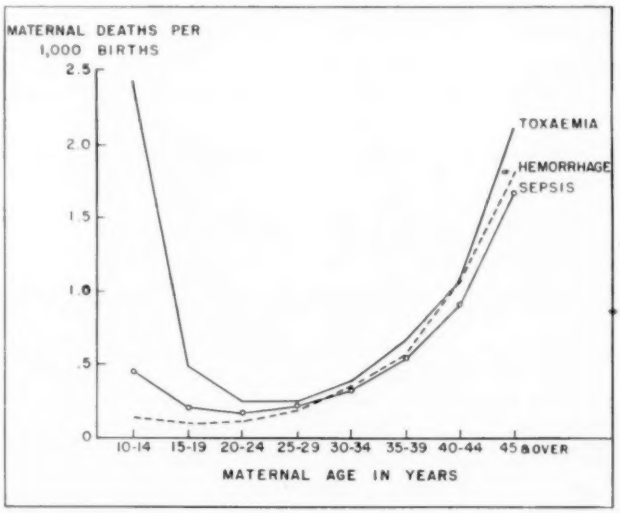

Fig. 2—Maternal mortality rates by age and principle causes, United States of America, 1945-1949.

THE YOUNGER MOTHER. The greater incidence of maternal deaths at ages under 15 years is predominantly a feature of toxemia of pregnancy. When toxemic deaths are excluded, maternal deaths for the age group under 15 years exceed but slightly those for ages 15 to 19 years. Mortality statistics are notoriously open to error because of inadequacies in diagnosis and reporting, to such extent that exclusion of recorded deaths from toxemia in all probability still leaves cases where toxemia was an important factor. The conclusion seems warranted that apart from an increased risk of toxemia, the youngest mothers experience no greater mortality during childbirth than women of 15 to 24 years, where the rate is lowest.

A number of reports[18,48,71,162] devoted to the clinical features of pregnancy and labor in girls of 16 years and under, suggest that the frequency of obstetrical complications is no greater than for mothers in general. Antepartum and postpartum hemorrhage, malpresentations, inertia, prolonged labor and the necessity for

surgical intervention are least frequent in this age group. Third-degree perineal lacerations are a possible exception[4]. Mortality figures seem, therefore, to express the comparative freedom from complications enjoyed by the adolescent mother.

National vital statistics do not separate the effects of age and of parity as determining factors in the greater frequency of toxemia in young mothers. Toxemia is known to be common in primiparae: some 70% of patients with pre-eclampsia are primiparae[2]. The greater incidence of toxemia in this youngest age group may reflect no more than the high proportion of primiparae. Most clinical reports either have no comparison group[44,185] or compare younger patients with general clinic experience[66,124,148], with consequent failure to differentiate between low age and primiparity. In one instance[124], where cases of toxemia are recorded by age of the patient, incidence was 42% at 13 years and only 16% at 16 years, while the proportion of primiparae was but slightly different, 100% and 96%. Another study[37] dealing solely with primiparae shows the incidence of both pre-eclampsia and eclampsia to be higher in the very young. Primiparity is one factor in the greater incidence of toxemia among young mothers, but is clearly not the whole explanation.

OLDER MOTHERS. An increased risk of disability and death is also associated with high maternal age but no single cause is outstanding, Fig. 2. Parturition in older mothers has had much clinical interest. Most of the earlier reports, dating from the comments of Mauriceau[128] in 1721, were brought together by Kleinwächter[95] in 1884, in an excellent summary of the literature to that date. Studies since then are concerned mainly with comparison of elderly and young primigravidae[68,131,137,154,178] although some deal with both primiparae and multiparae[26,145a,b]. The first group of reports and those parts of the latter that deal with primiparae have special value in that they permit comparison of age with parity constant. The evidence is best presented through separate consideration of individual clinical groupings of disease or disability.

After the initial high rates among the youngest mothers and the favorable situation at ages 20 to 29, the incidence of toxemia of pregnancy increases steadily with maternal age. The increase at older ages can scarcely be secondary to a parity effect in view of the decisive proportion of primiparae among patients with toxemia. Further support is had through comparison of old with young primiparae; a higher incidence of toxemia is usual in the older group[4,37,49,188].

Several authorities recognize a high incidence of placenta previa and abruptio placentae among elderly mothers[26,37,188]. Both conditions have long been recognized as a function either of high parity or of relatively advanced age. Penrose[146,a] and Kalmus[91] compared groups of such cases with normal births from the respective hospitals, and came to the conclusion that the incidence of the central variety of placenta previa is primarily a function of age, while the lateral and marginal varieties, and accidental hemorrhage, are associated mainly with high parity.

Postpartum hemorrhage and retention of placenta in primigravidae appear to increase with age[4,37,49,111], but conflicting reports exist[150]. Thompson[179] considers the main contributing factor to be the greater frequency of myomata among elderly primigravidae.

Although puerperal infection is an important cause of maternal disability and death, little information has been gathered on a possible association with age. National mortality statistics (Fig.

2) reveal a marked association, at least for deaths, with the higher rates centered in the older age groups. The explanation may rest in the greater frequency of operative procedures for high-age high-parity mothers. The puerperal infection rate of elderly primigravidae has been found high when compared with that of all other patients of a clinic[101]. Other studies concerned only with primigravidae, sometimes give higher rates for puerperal fever for younger and older mothers[37]; and sometimes no variation[49] in frequency of febrile attack with age.

Criteria for determining efficiency of uterine action are difficult to establish. Some observers report no evidence of deficient uterine action among elderly primigravidae[78], while others find inertia a frequent complication[75,137,150,179]. Length of labor is commonly employed as an index of uterine efficiency[26,35,68]; and as such is consistently no longer for the elderly than for the young[131,149,188]. However, the greater frequency of operative interference in older mothers tends to discount the value of this measurement. The frequency of premature labor, as measured by length of gestation, appears to be not at all[51a] or only slightly[92] related to either age or parity.

Almost no attention has been given to the influence of age at childbirth on the subsequent medical history of the mother. To what extent, for instance, is the risk of permanent circulatory damage after toxemia dependent upon age? Variations with number of previous children are well established for cancer, but data are fragmentary[140] on the age of the patient when these children were born.

Maternal Age and the Infant. Basic epidemiologic method has to do with separation from whole populations of groups of persons having a common characteristic, and a search then for the causes that determine such circumstances. Evidence has been given that age is a factor in the risks that women experience in childbirth. If maternal age is indeed an epidemiologic principle, then other fractions of the population are to be recognized as subject to influences directly or indirectly related to that attribute. The children born to mothers of different age suggests a part of the population as important as mothers themselves. The test of the hypothesis is first through examination of characteristics manifest at birth, and secondly through qualities that become apparent in later years.

Fetal and Infant Deaths. The majority of fetal deaths occur during the first months of pregnancy, under circumstances where knowledge of cause is least well defined. Estimates of the proportion of pregnancies ending in abortion range from 12 to 44%[117]. As a consequence, it is not surprising that few reliable data are at hand on association of these events with maternal age.

ABORTION. Kopp[98] noted that abortion increased from 10% in first pregnancies to nearly 50% in pregnancies after the sixth. In a number of studies of patients attending birth control clinics, the incidence of illegally induced abortion increased markedly with birth order and duration of marriage, no change being noted in the frequency of spontaneous abortion[171,172]. Wiehl and Berry[191] also reported association between birth order and induced abortion, but not for spontaneous abortion, in a group of multiparous women. That these results are an expression of highly selected groups is suggested by an increase of abortion with maternal age in a series of planned pregnancies in which it was thought that criminal abortion was unlikely[183]. Two small series[20,165] of patients aborting hydatidiform moles provide an example of a single cause of abortion with

demonstrated relation to maternal age for a less highly selected population of women from a general clinical experience. The study is yet to be made of the total of abortions in a representative population with adequate controls.

STILLBIRTHS AND NEONATAL DEATHS. Stillbirths and neonatal deaths are conveniently grouped together, for the reason that many conditions contribute to causation in common, and most studies make reference to both. In 1874, Ansell[3] noted that for first pregnancies the risk of stillbirth was more than double that for later births. The increased risk extended into the neonatal period, but for ages thereafter mortality for the firstborn was less than average. For 14,968 births occurring in Baltimore[156] in 1915, rates for stillbirths and neonatal deaths were high in first parities and young mothers, were at a minimum at ages 25 to 29 (2nd and 3rd births) and became increasingly greater with increasing parity and maternal age, the two influences being independent. These important observations have been confirmed in the United States by Woodbury[196], Gould[56] and Yerushalmy[200a,c], in Canada by Robinson[155], and in Great Britain by Burns[25], Sutherland[175a,b], Baird[5], and Gibson and McKeown[51b].

By constructing separate trend lines for stillbirths and for neonatal deaths, the general behavior of the two events in relation to age and parity is seen to be similar, although not identical. Both trend lines decline as parity advances from first to second births, somewhat more so for stillbirths than for neonatal deaths. If the initial decrease already noted is judged on the basis of age, the reverse holds, with little effect evident on stillbirths and a material drop in neonatal deaths[156]. After the minimal levels established at ages 20 to 29 years, or parities 2 and 3, rates for both neonatal deaths and stillbirths become progressively greater, whether judged by parity or by age. For stillbirths, the relationship is stronger with age than with parity, while for neonatal deaths parity is the dominant factor[51b,196,200a]. Interestingly enough, the fall in stillbirth rates in Canada[155] between 1927-30 and 1940-43 has been largely the result of lesser rates at the lower maternal ages; the rates for women over 30 years have remained much the same.

Mothers have so evident a connection with the process of childbirth that the essential contribution of fathers is often overlooked. Yerushalmy,[200b] examining the association of stillbirth and neonatal deaths with age of father, found rates to be greater for children of younger and older fathers. This association held when judged in relation to each 5-year maternal age group. His results are not entirely conclusive, since the 5-year maternal age groups used do not entirely eliminate the maternal-paternal age association. In addition, the associations between birth order and maternal age and between maternal and paternal age were considered, but no allowance was made for the evident association between age of father and birth order. Sutherland[175b] in a larger material from New Zealand, found no association of stillbirth rate with age of father at constant maternal age, except that the rate was high for mothers under 20 when the father was under 21. This single inconsistent result again may have explanation in a correlation between age of father and birth rank, which probably exists even at constant maternal ages.

POSTNEONATAL INFANT DEATHS. Fewer data are available on the relationship between parental age and deaths after the first month of life. The early studies of Rochester[156] and Woodbury[196] reveal associations with both birth order and maternal age for "causes peculiar to early infancy," and

also for other causes of infant death. The associations were, however, less marked for "other" causes than for causes peculiar to early infancy. More recent investigations have failed to confirm these findings. Burns[25] found that the characteristic relationship with birth order for neonatal deaths was not maintained after the first month of life. Gibson and McKeown[51b] found little association with birth order or maternal age for later infant deaths except for those ascribed to infection, the rates for which increased with increasing birth rank and decreased with increasing maternal age. Furthermore, when observations were limited to children in more favorable economic circumstances the trend with maternal age was eliminated and that with birth rank reduced. Differences in the extent and causes of infant mortality in the two periods seem a reasonable explanation for some of the inconsistencies between findings of earlier and later studies.

Biologic Attributes of the Infant. Of a variety of characteristics and more than a few morbid conditions of man conceivably associated with age of the mother, none is more tangible than the number of offspring of a given pregnancy. The search now is for evidence of maternal age as a determining factor in such events.

MULTIPLE BIRTHS. The incidence of twin pregnancies increases with maternal age through all age groups until 35 to 39 years and then falls[34]. According to data published by the U. S. Bureau of the Census[24], incidence also increases progressively with birth order and continues to increase at least until birth order 10. The data are of such nature as to permit the effects of birth order and maternal age to be separated, and to recognize each as an independent variable with birth order having somewhat the greater value. Despite this evidence, the idea is still common that parity is of no significance.

If twins are divided into monozygous and dizygous sets according to the Weinberg[189] method which depends upon the proportion of unlike to like sexed sets, dizygous sets show an association with maternal age, whereas monozygous do not[87a,88,187]. A differentiation of 495 twin sets on the basis of physical characteristics[61] gave an association with high maternal age for dizygous sets and no effect for monozygous twins. Guttmacher[65] separated monozygous and dizygous sets by placental examinations and reached similar conclusions. He also noted dizygous sets as commoner at high parities. Despite his conclusion that monozygous twinning has no association with either age or parity, the data given show some association with both. The relation, however, is less marked for monozygous than for dizygous sets.

Yerushalmy and Sheerar[201] determined individual effects of age and parity for both monozygous and dizygous twins. With the differentiation of types of twin by the Weinberg method, and with birth rank constant, the maternal age effect was much stronger for dizygous than for monozygous sets. With maternal age constant, the frequency of both types increased with birth order. At ages under 25 years, the rate of increase with increasing birth rank was much greater for like sexed twins than for unlike sexed, whereas after 25 years the reverse was true. Maternal age would thus seem to have a more striking influence on dizygous than on monozygous twinning, but that this is the single factor involved, as so commonly assumed, is scarcely warranted by the incomplete data at hand.

Triplets also show an association with maternal age which agrees with expectation calculated on the assumption that monozygous triplets are inde-

pendent of maternal age while dizygous sets increase with age of mothers[88,187]. Adequate separation of age and parity by type of triplet is, of course, still more difficult than for twins.

SEX RATIO. Variations in the proportion of male to female births according to maternal age were suspected[12] as early as 1878. Vital statistics of many countries show the percentage of male births to decrease as maternal age increases, a situation that holds for the United States[30,119,129,159], Great Britain[109,127], a number of countries of continental Europe[190], Australia[96], and Japan[176]. Decreasing sex ratio with increasing age of father has also been recorded[139]. However, a number of observers have noted a decrease in sex ratio with increasing birth order[30,96,107,159], a matter that has led to much debate as to whether the association is more with birth order or with maternal age. Recent vital statistics of the United States[122] demonstrate that while the sex ratio for livebirths falls consistently with birth order, there is no consistent trend with maternal age when birth order is kept constant. Fig. 3.

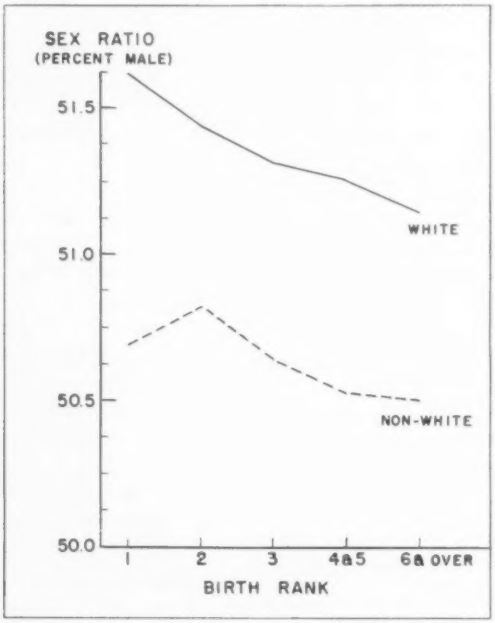

Fig. 3.—Sex ratio of livebirths according to race and birth rank[122], United States of America, 1942-1949.

The sex ratio of stillbirths is high in younger and older mothers, and also at high and low parities[122], but the relative importance of age and parity has yet to be ascertained. Most of the change in sex ratio of stillbirths as related to maternal age can be accounted for by changes in the distribution of stillbirths by cause at different maternal ages, individual causes having different sex ratios[109]. These facts support the prevailing hypothesis that the known variations in livebirth sex ratios result

from differential elimination of sexes by some common cause or causes of early fetal death, which are related to birth order. Variations in sex ratio at conception according to birth order, or in a mechanism by which sex is determined after conception, are other explanations judged unlikely on present evidence.

The phenomenon of a varying sex ratio is not restricted to man. Changes with either birth order or maternal age, rarely separated in studies on experimental animals, have been noted in mice[32,74], rats [93a,b,94] and several domestic animals[192].

BIRTH WEIGHT. Weight at birth was perhaps the first characteristic of the infant to draw suspicion of an association with maternal age or with birth order. General agreement now holds that first-born children tend at birth to weigh less than second-born, and that birth weight increases with parity. This behavior was noted in 1864, by both Hecker[76] and Duncan[40]; and has since been amply confirmed[62,70a,b,144b,161]. Several anthropometric measurements, such as body length, head size and several muscular measurements, have also been shown to be smaller for firstborn than for later children[45].

The superiority of later born children is not long maintained. Many years ago[17], first-born children were demonstrated consistently to exceed later born in stature and weight from the 6th year to adulthood. Similar findings have been reported recently for 1 year-old[79] and 3 year-old children[110].

Opinion on relationship of maternal age to birth weight is much less uniform than for birth order. Duncan[40] was one of the first to suggest that age exerted a greater influence than parity, although others of the time considered the effect of age to be small[47,69]. Other studies[45] brought out that weight as well as other measurements is slightly less for births occurring at the extremes of reproductive life, irrespective of parity. The first[116] of two recent and comprehensive studies on the relative effect of age and parity has demonstrated for some 22,000 births that weight increases regularly with parity when age is fixed; but that no consistent relationship between weight and maternal age is apparent when parity is fixed. In another series[92] of 14,000 infants, birth weight increased with parity; but with parity constant, a slight but significant negative correlation existed between birth weight and maternal age. The latter observation is in agreement with the findings of Kleinwächter[95] in 1884, that mean weight of first-born infants falls slightly with increasing age of the mother. Evidence has been introduced earlier in this review to show that the frequency of premature birth is not related to age or birth order. Variations in infant weight are thus not the result of shorter gestations of first pregnancies[33,51a].

CONGENITAL MALFORMATIONS. Association between maternal age and congenital malformation is an area better explored than most. Shuttleworth[166a,b] in 1886, and again in 1909, pointed out that mongoloid infants tended to occur at the end of long families, with some one-third born of mothers over 40 years of age. Similar experience[103,105] was reported by other early writers[141, 170,180]. In 1933, Jenkins[87b] assembled cases from several of the larger reported sources of mongolism[22,53,142,184] and compared them with normal births occurring in the United States and in the Netherlands. The result was clear cut evidence of a marked excess of mongolism in high maternal age groups. When maternal age was kept constant, birth order and age of father were of no significance. Comparison of maternal age, paternal age and birth order of mongols with similar data on normal sibs led Penrose[146b,c,d] to the same conclusion. Several confirmatory

reports have appeared in the past 15 years[8a,11,16a,157]. The frequency of mongolism, as determined directly by Carter and MacCarthy[28] from the known number of mothers in various age groups delivered in a number of London maternity hospitals, is illustrated in Fig. 4. The data are in close agreement with those of Penrose, obtained by indirect methods.

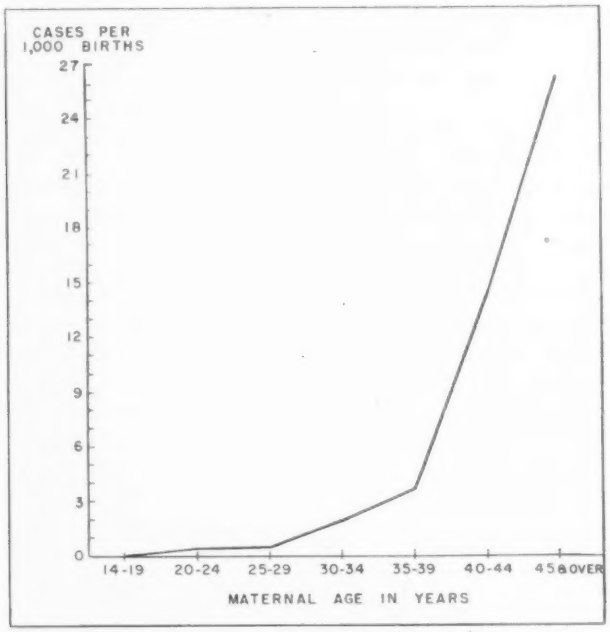

Fig. 4.—Cases of mongolism per 1,000 total births in selected London maternity hospitals; from Carter and MacCarthy[28].

Demonstration of a maternal age effect in mongolism naturally led to search for similar relationships among other congenital malformations. Studies based on grouped malformations have given conflicting results. Murphy[134a,b] reports a marked excess of malformations at high maternal ages, but the results are discounted in large degree by the fact that families were incomplete at the time of study. The reports of Malpas[123], Buchi[23], Hegnauer[77], and others involving lesser numbers[38,102] indicate a greater incidence with advancing maternal age. Carter[27] found no residual maternal age effect on malformations when patients with mongolism were excluded. In a large series[197] of malformed children with the condition recognized at birth, the frequency of fetal and neonatal deaths was greater with advanced maternal age, but maternal age had no relation to frequency of malformations for children surviving that period.

Study of various combinations of grouped malformations, whether selective or with attempt toward inclusiveness, is a useful preliminary to indicate more profitable lines of inquiry. As a means of acquiring definitive information, the promise of result is about that to be anticipated through examination of all stillbirths or all infant deaths as

a group. Much of the divergent opinion is to be explained by variations in the material studied, in the weighting of a group with some particular malformation, or in the choice of malformations included within the group.

Once a particular biologic characteristic is identified in connection with grouped malformations, the next procedure is to examine the individual entities, insofar as they can be recognized. Malformations that appear to be clinical entities give no guarantee of an identical etiological derivation. Nevertheless, the markedly divergent sex ratios and other features that have been demonstrated for individual malformations, suggest that these clinical entities are a closer approximation to etiological units than is to be expected from such a group as "malformations in general." They justify individual study. The rarity of some conditions introduces difficulty in assembling adequate numbers of cases for analysis. Some of the commoner defects have been studied in detail.

Malformations of the central nervous system account for somewhat more than half of all stillbirths and infant deaths attributable to malformations[151a]. In a study of all malformations among 13,964 births in a maternity hospital[123], anencephalus and hydrocephalus were most frequent at higher maternal ages, while spina bifida had no association with age. The numbers naturally were small. Other series having the same limitation of small numbers[19] or with unsatisfactory controls[147] have shown no association with age.

In a comparison of 144 grouped cases of anencephaly, spina bifida and hydrocephalus with their normal sibs[148,c], maternal age was related to incidence. After correction for the effect of maternal age, occurrence was somewhat in excess in the first birth rank, and at birth ranks 7 and over. For 2,922 malformed children identified among some 160,000 births in Copenhagen[23] the frequency of hydrocephalus, spina bifida and anencephalus increased with maternal age. The most satisfactory series thus far reported compares deaths in Birmingham[151a] from malformations of the central nervous system with controls drawn from the birth registers of the city during the same period. Hydrocephalus was more frequent with advancing maternal age, while anencephalus and spina bifida were not. The latter two conditions were commoner among first births and for births after the sixth, irrespective of maternal age. Changes in fertility of mothers of malformed children were not a contributing factor[151b].

The evidence relating harelip and cleft palate to maternal age is both incomplete and contradictory. One study[182] recognized an excess of patients in early birth ranks and at early maternal ages. An association with either age or birth rank was nonevident in two others[46,57]. All three enquiries had the common characteristic of unsatisfactory controls. Still another study[114] ended with the conclusion of no association between these anomalies and maternal age; but the data show a significant excess of patients at parental ages over 30, compared with the cited controls. A Danish experience[23] of greater incidence with increasing maternal age has had confirmation in Great Britain[121], at least for harelip, and harelip with cleft palate. Isolated cleft palate did not appear to show a greater incidence at high maternal ages. The association of harelip with age is of the order evidenced by hydrocephalus, and much less than that of mongolism.

Association of congenital heart disease with maternal age has been reported[23,100,123], but a larger and more representative series[120] showed no re-

lationship when defects associated with mongolism were excluded.

Collected information[16b] on 303 cases of achondroplasia from widely scattered sources, gave evidence of significantly more mothers aged 30 years or over of achondroplastic than of normal infants representing births in the United States. Study of smaller but more homogeneous groups of cases from Denmark[132] and from Great Britain[100] has substantiated these conclusions. From 18 reports of births of achondroplasiacs to achondroplasiac mothers[64] maternal age seems not to be a factor in familial achondroplasia, in contrast with the recorded behavior for sporadic or isolated instances. Of related interest is the recent report[146j] of lower mean maternal age for sibships of two or more mongoloid children compared with single such births.

Other studies have indicated association of maternal age with exomphalos[118c], talipes equino-varus[23], esophageal atresia[84] and congenital cranial osteoporosis[153]. The high percentage of first-born infants among patients with infantile pyloric stenosis has not been related to low maternal age[118a].

The association of mongolism with maternal age is so definite that further work would seem most profitably directed toward identifying factors which are contributing to the association, rather than to confirming its existence. Harelip, harelip with cleft palate, hydrocephalus and achondroplasia appear to have a less definite association. Suggestive observations on exomphalos, esophageal atresia, osteoporosis and talipes require confirmation. Investigation of age effect for all of these malformations, could well be extended. Age of father, for instance, has not been examined for any except mongolism. Many of the less common and less outstanding malformations have yet to be submitted to the simple primary test of a relationship with maternal age.

Maternal Age Effects Evident After Infancy. Maternal age has been examined for association with some few diseases and for some biological characteristics not apparent at birth but becoming evident later in life. The ability to perform intelligence tests has had particular attention, and an excellent summary[181] of the earlier literature is available.

Francis Galton[50] noted, in 1892, that the parents of a group of eminent men were considerably older at the time these men were born than are most parents, an observation corroborated by others[42,202]. An excess of first births has been noted among Italian professors[52], for persons listed in American Men of Science[29] and for "child geniuses"[177]. The significance of all these reports is doubtful. The criteria of eminence are at best arbitrary, the statistical methods employed are frequently questionable, and in the last analysis, no certain means are at hand to distinguish ability from opportunity to become eminent.

At the other end of the scale, Mitchell[130], as early as 1866, noted relatively 4 times as many mental defectives born to women over 40 years of age, as to mothers under that age. No irregularity in order of birth was said to characterize a group of some 10,000 retarded children in public schools[36]; but re-examination and analysis[181] of the data gave evidence of a gradually decreasing proportion of defectives with increasing birth order.

In studies designed to test a relationship between ability to perform intelligence tests and birth order, the average of intelligence quotients was higher at later birth orders[31,115,168,181,194], although some authorities[90,174] dissent. Less consistent results are had in relating this characteristic to maternal age; and indeed some investi-

gators[181] report lack of definite correlation between intelligence quotient and maternal age. A seemingly positive result from examination of 4,000 school children held even with family size constant, but only for those of superior economic status[133], which suggests that social environment is as much an influence in the correlation as are biological factors.

Other than manifest deficiency and genius, mental abnormalities have had little attention in respect to maternal age. Havelock Ellis quotes Marro[125] as finding a disproportionate number of criminals and insane among the children of fathers under 25 and over 40 years of age, with the disproportion more marked for the insane than for criminals.

In spite of all that has been written about the importance of family life and of early impression in the genesis of psychoneurosis and personality disorders, few objective data are available on maternal age as a presumptive influence. Patients with mothers over 40 years of age at the time of birth constituted 9.4% of 1,000 psychotics, as against 3.6% for 222 psychoneurotics and 3.9% for all births of the U. S. Birth Registration Area[6]. Another recent study[138] determined distributions of birth rank and maternal age of 500 psychoneurotics, excluding patients with florid psychoses, and using 500 patients in a general hospital as controls. The higher maternal ages and the higher birth ranks had an excess of affected persons. The association with maternal age was somewhat more definite than with birth rank, but attempts to separate the two were inconclusive.

The association of cerebral palsy with birth order and maternal age is much the same as that observed in stillbirths and neonatal deaths[108]. The findings are in agreement with other, smaller groups of cases[43,146b]. These results are not surprising in that many causative factors are common to the three situations.

The average age of women delivered of infants later recognized as epileptic[146a] was somewhat greater than the corresponding average age of mothers of mental defectives. Other studies noted a greater risk of so-called idiopathic epilepsy at maternal ages over 40, less markedly under 20 years[8a]; while a slight excess of observed over expected was characteristic of later birth ranks[21].

Limited evidence exists of an influence of maternal age on length of life. In 1901, Beeton and Pearson[9] recognized mean expectation of life to be 4 years longer for early children than for later born brothers and sisters. Dublin and Marks[39], examining insurance records for a relationship between expectation of life and age of parents, observed that quality as positively correlated with age attained by parents. There was one consistent departure from this general behavior. Younger insurance risks born when their parents were of more or less advanced age showed high ratios of actual to expected deaths. They state "This characteristic has been noted in earlier investigations also, and in our judgment, it indicates a generally inferior vitality in such children. The causes that bring about a high maternal mortality among older mothers and for their infants probably affect the vitality of the children who survive, although the economic and other advantages of longer established families would seem to act favorably on such children."

Material drawn from Scandinavian genealogies[86] demonstrates that mean length of life decreases progressively with increasing maternal age, but without association with paternal age. The association was not limited to infants and young childen. At all ages up to 45 years, expectation of life was higher

for the children of young mothers. Both males and females followed the trend.

Maternal Age in Experimental Animals. The main advantage of studies of maternal age in the experimental animal is that observations are not limited to characteristics present at birth. Investigation of the range of effects that occur throughout life is practicable, because the life of the animal is within usual experimental limits. A disadvantage is that animals are usually mated throughout the reproductive period and at each physiological period of heat. As a consequence, the effects of advancing age and increasing litter order are difficult to separate. This reservation is to be borne in mind during the following account.

As in man, fertility and fecundity of animals are related to age. Pearl[143] in 1913, was so impressed with the complete breeding history of a ewe, published in a farming journal, that he republished the data to support the principle previously stated by Marshall[126], that fecundity starts from sterility, rises rapidly to a high point and then gradually falls off to sterility. The interval between litters cast by rats, the first usually at age 3 months, is shortest at about 7 months of age, and lengthens gradually thereafter to the last litter at about 18 months[93a]. Estrous cycles of old mice tend to be lengthened and irregular[63]. The number of offspring per litter also follows the same trend[13a,b], reaching an early maximum in the second or third litter, and thereafter falling off with advancing maternal age, a phenomenon that holds for a number of different strains of mice[63,135] and also for rats[93a,b]. The number of corpora lutea of pregnancy increases progressively[112a] with birth order, at least until the tenth litter, and the reduction in viable offspring occurring after the second or third litter presumably is due to death of the ovum at some time between liberation from the ovary and the later stages of pregnancy.

Although the number of corpora lutea per pregnancy is known to increase with litter order rather than with age[112b], no satisfactory separation is known of age and birth order as determining factors for numbers of viable offspring per litter. Some fragmentary data reported by Bittner[13b] suggest litter order as the more important.

With inbred strains of guinea pigs the percentage of white in the coat increases and the incidence of polydactyly decreases with advancing age of the dam[198a,b,199]. The association with polydactyly is probably the most striking relation with maternal age yet observed for any species, polydactyly decreasing from 83.3% in the offspring of mothers aged 3 months to 9.6% when the mother is 17 months old, a result confirmed by others for guinea pigs[99] and also for mice[81]. Numerous other instances of an influence of maternal age or birth order on the expression of presumably genetic traits among inbred strains of mice, include such conditions as harelip[152,169], a peculiar anomaly of the external ear[97], malformations of the vertebral column and ribs[58], and the condition of eyelids open at birth[73]. The lesser frequency of spontaneous leukemia of mice with increasing age of mother[113] has resulted in assumption of a "maternal resistance factor" that increases with age[106].

Methylcholanthrene, injected into inbred strains of mice, predisposes to fibrosarcoma. A series of studies by Strong demonstrated that the latent period between the injection of the carcinogen and the appearance of the tumor was longer for mice belonging to early litters[173a], than for the progeny of later litters of the same parents. Total incidence of tumors was lowest for mice of early birth orders. Another and distinct strain of mice gave the

opposite behavior, an increasing latent period with increasing litter rank[173c]. Further investigation of the first strain indicated that the association was present only in females, the latent period for males remaining the same in all litters[173d,e]. Following appearance of the tumors, mice born in early litters showed a shorter survival time,[173b,h] and more frequent invasion and metastases,[173e,f] than their later born siblings. These results were interpreted as indication of some factor influencing tumor susceptibility, of varying concentration with age and capable of transmission by the mother to the offspring. Of greatest significance is that this factor is apparently cumulative through successive generations[173e,f]. Sub-lines of mice established respectively by breeding from late and from early litters differed markedly from each other in their latent period for fibrosarcoma.

Particular strains of mice susceptible to cancer, harbor an agent[13c] in the milk of cancerous mothers which when fed to the offspring induces breast cancer later in life. The agent is most effective when administered to offspring early in the neonatal period. Host resistance is acquired with age. The agent is filterable[13d,e], is of the order of magnitude of a virus[186] and is antigenic[1,59] qualities which reasonably permit it to be regarded as a virus. The agent is apparently not transmitted to mice born in early litters, but is transmitted to later litters of the same mothers, with a consequent increased incidence of mammary gland tumors in advanced litters[13f]. Whether or not this factor is, like Strong's fibrosarcoma factor, cumulative through successive generations, remains unknown.

With advancing age the blood serum of chickens develops the power to neutralize or modify the viruses of chicken sarcoma and endothelioma[41a,e]. A similar situation occurs in rabbits with regard to fibroma virus[41c] and in the duck[41e], pheasant, turkey, and guinea fowl[41b] with regard to the Rous sarcoma virus. Not only is age of the host a factor in the clinical progress of these diseases but the age of a donor animal may also determine whether or not the agent will invade. If invasion is successful, the clinical nature of the disease in the recipient is modified[41d]. Whether the resistance factors, which clearly vary with age, are also transmissible to the offspring would be useful information.

Maternal age or parity has also been studied in relation to more complex biological characteristics and to infectious diseases. Thus the percentage of mice born dead[135], and also the percentage dying within 30 days of birth, was found to increase with advancing maternal age. Russell[158] found the highest incidence of juvenile diarrhea of mice among animals of first litters. Rams, which were the progeny of young ewes, and also those sired by lambs or young rams, achieved the highest average prices and the lowest rejection rates in New Zealand stock markets[7].

Lower orders of animal also give evidence of maternal age effect. Young workers born to immature female ants[54] were small and short-lived, compared with later offspring of the same mothers. On the other hand, the rotifer[89], as the progeny of older parents, did not live as long as those born of young parents. Lansing[104a], has demonstrated clearly the presence of a nongenic factor that influences the longevity of this multicellular parthenogenetic aquatic organism. Activity of this factor is associated with age of the parent. In two species of rotifer, length of life was related to age of parent when the egg was produced, and the presence of an "aging factor", which increases in the body of the parent and can be transmitted through the egg to the off-

spring, is postulated. This aging factor, it was found, could be concentrated by repeated selection of eggs from older animals through a series of generations, with progressive decrease in life span and eventual extinction of the "line" or "orthoclone." On the other hand, repeated selection of eggs produced at the onset of reproductive life led to the establishment of orthoclones in which longevity was increased from 24 days up to 104 days[104b]. Moreover, these trends were reversible, and orthoclones which were on the point of extinction could be revived by selection from them of eggs from newly matured animals. It is furthermore suggested that this aging factor is in some way linked to growth regulation, since the change from longevity-increasing to longevity-decreasing eggs occurs rapidly and coincides with the time of cessation of growth.

The influence of age of mother on what might be called the social environment of the offspring has had limited study in animals. As early as 1917, King[93a] noted that, "not infrequently the offspring of old mothers (rats) were born dead or soon died from neglect as the mothers seemed unable to suckle them." The mother rabbit evidences variation with age in the capacity or desire to build nests and in the aggressiveness of the mother towards her young. The form of these variations differs with strains of rabbit[160]. Marked changes with age have been noted in the percentage of litters eaten by cannibal mice[72] of various strains.

Factors influencing many characteristics of a variety of experimental animals have been revealed through observations on maternal age. That more work has not been done on the separation of age and birth order is somewhat surprising. Postponement of first litter to older ages is a simple matter. Many of the problems of animals have a direct application to man, such as interval between births, induced and natural infertility, and the effect of local and general maternal disease. Investigation through human material is only by arduous collection of past or completed events, often from sources difficultly accessible, and commonly lacking detail. In the laboratory such factors can be manipulated with much facility; and what is more important, they can be subjected to adequate control.

Interpretation of Maternal Age Effect. The primary demonstration that an association exists between age of mother and either a specific disease or a recognized biological characteristic, is no more than a first step in understanding the meaning or significance of that relationship. Furthermore, the mere fact that each of two conditions is influenced by maternal age bears no implication that causation in both instances is similar or even in any way related. These facts are no deterrent, however, to accepting examination for association with maternal age as an epidemiologic principle. Race, for instance, is well established as a primary epidemiologic variable, but the multiplicity of factors responsible for racial variations in frequency of disease could hardly be more diverse. Associations of morbid processes and other conditions of the mother with maternal age, as distinguished from those evidenced by the infant, are now considered separately. Interpretation is clearly different for the two.

MOTHER. The elderly mother, and especially the elderly primigravida, enters pregnancy with evident handicaps. Pre-existing hypertension[35,78] and myomata[4,101] are undoubtedly more frequent[150,188]. The first condition may well be one of the factors in the high incidence of toxemia. Randall and Taylor[150] report a high incidence of thyroid disease in the elderly. Cardiac

disease is probably more frequent among elderly multiparae[78], but for elderly primiparae the incidence is variously reported high[4,26] and normal[101,188]. A low incidence of heart disease in elderly primigravidae is not as paradoxical as it may seem, since many cardiac patients die young and survivors are less likely to marry late and become elderly primigravidae[188].

A dissenting opinion[37] can be found in most medical matters that involve judgment rather than factual evidence; but most authorities agree that contracted pelvis is more common among elderly primigravidae than with younger mothers. The usual explanation is that an android type of pelvis is a frequent feature of the general "sterility syndrome"[85,179]. Evidence that elderly primigravidae experience an onset of menses later than do women in general[154], and that menstrual flow is often irregular[111] tends to support this view. An established correlation between late marriage or delayed pregnancy and reproductive inefficiency would contribute to improved understanding of the high morbidity and mortality rates associated with pregnancy among older women.

Some of the conditions listed among maternal effects, notably toxemia and placenta previa, could be classed with equal validity among fetal influences. Other characteristics regarded as fetal, such as multiple pregnancy and gross fetal malformation, may also contribute to the recognized variations in maternal risk that come with increasing age.

Most of the obstetricians so liberally quoted believe that the obstetrical risks faced by the elderly primigravida have been overemphasized in the past, and are indeed little greater than for the younger primigravida. This view is not inconsistent with the impressive list of conditions noted as commoner at higher maternal ages. An association having distinct causative significance may be relatively trivial from the clinical point of view, because of the comparative rarity of the pathologic condition.

OFFSPRING. Geneticists have long been concerned with associations between infant characteristics and maternal age, principally as a means to distinguish influences of environment from those of inheritance, since genetic constitution is not affected by age[80]. A condition has always been introduced that the frequency of mutation conceivably varies with maternal age[118b]; particularly so in view of the recent observations that all ova are not preformed at birth, but that ovogenesis occurs throughout adult life[164]. However, mutations can be regarded as environmental, being not dependent on genetic constitution of the parents. The validity of maternal age association as an indicator of environmental influence remains. In addition, since explanations of relationships with age, of the order of those now known, would require mutation rates far in excess of any thus far measured or believed to occur, this proviso has of late been treated lightly. In mongolism, for instance, almost the whole of the disease (incidence about 1.3 per 1,000 births) would have to be explained in this way.

Recent experimental work introduces further difficulty in attempts to distinguish attributes derived through inheritance and those arising from environment, in that biological inheritance seems no longer restricted to purely genetic considerations. The work of Sonneborn[167] introduces the view that characteristics are transmitted from generation to generation by means unexplainable in Mendelian terms. Whatever the mechanism of this type of inheritance it varies with maternal age and birth order[104,173] in some instances. The possibility is reasonably entertained that man also has non-genic inherited qualities related to maternal

age; but the length of generations in man makes it unlikely that existence of such factors will be demonstrated within the immediate future.

A suggestively more profitable line of inquiry is an attempt to measure those unfavorable environments connected with particular maternal ages. To investigate all such situations is a task outside practicability. Sufficient evidence has been introduced to indicate the more likely modifiers of the fetal environment. A practical division is between environment before birth, *in utero*, and postnatal environment.

The significance of maternal age as a factor in the changing intra-uterine environment has been studied almost exclusively in mongolism, for the reason that this condition provides in man the most striking instance of an association with age. Hormonal alteration and the frequency of disease of the maternal reproductive tract have had the major attention. In Ontario, areas of high incidence of thyroid disease were found to coincide with areas of high incidence of mongolism[136], and the incidence of recognized thyroid disorder during pregnancy was somewhat higher for mothers of mongoloid infants than of other mental defectives. Benda[11] reported 10 cases of thyroid deficiency and goiter among the mothers of 75 patients with mongolism, and Williamson[193] reported one mongoloid child among the offspring of 48 mothers treated for severe hyperthyroidism during pregnancy. Thyroid disease clearly is more frequent with advancing age, but the association with mongolism is not striking and the number of patients thus far studied is small.

A high incidence of disease of the reproductive tract among mothers of mongoloid infants has been better established. The collected results of individual studies[10,11,163] include 44 instances of hemorrhage during 216 pregnancies that resulted in mongoloid infants[83]. On the basis of further detailed case histories Ingalls[82a,b] suggests that the search for possible etiologic agents be centered on the sixth to ninth weeks of fetal life and that a considerable variety of agents acts at this time. He has been impressed by the frequency of uterine retroflexion among mothers of mongols[82c], a view that has support in that 26 of 99 such mothers had a significant degree of retroflexion or prolapse of the uterus, while only 5.5% of 248 mothers of normal infants had similar abnormalities[163]. Disorders of the reproductive tract are expectedly more common in the higher age groups. More evidence is needed that for a given maternal age such disorders are unusually common in mothers giving birth to mongoloid infants.

Worcester, Stevenson and Rice[197] found greater numbers of abnormal placentae with increasing maternal age, but no unduly high incidence of abnormal placentae in relation to malformed infants. Better information on the inherent causes of abnormal placentae would aid in evaluating this suggested mechanism in genesis of malformations.

Age of the mother conceivably stands in relation to age of the ovum, either through aging within the follicle or through delay in transmission to the site of fertilization. Delayed fertilization is known to result in a high incidence of deaths and abnormalities in animals[14,15] as brought out in a recent review by Witschi[195].

Antigenic incompatibility is advanced by Penrose[146b] as a possible factor in maternal age effect, on the assumption that immunity develops in better degree in mature than in immature animals; and as a consequence the elderly mother is more prone to develop transient immune reactions against the embryo. This idea has another aspect. Resistance to infectious disease increases generally with age,

at least within the reproductive period and for those diseases characterized by an enduring immunity. Likely explanations are through better ability to produce antibodies and through increased opportunity for contact with infectious agents. Malformation due to infections during pregnancy would thus presumably decrease with advancing maternal age.

The age of the maternal parent as a feature of postnatal social environment of the infant, and a consequent factor in developmental characteristics, is another kind of problem. Separation and evaluation of this attribute from all other socio-economic factors is a matter so difficult as to have been scarcely touched upon. Add the further complexities inherent in the biologic and physical environment of the developing infant and the situation is more than baffling to the investigator who would seek, for instance, to explain an association between intelligence quotient and either birth order or maternal age. In experimental animals[72,160], age of mother is known to affect the social inter-relationship of mother and progeny. There is every reason to believe that the same holds for man. Additionally, age of mother is associated potentially with socio-economic status, maternal physique, intelligence and education of the parent; and with nutrition and other influences acting on the infant. Factual evidence on the value of these variables in relation to maternal age, and as a feature of postnatal developmental characteristics of the infant is in a rudimentary state.

Summary. Evidence derived from a wide range of diseases and disorders of mothers and infants supports maternal age at childbirth as a significant epidemiologic influence in mass disease of man. The effect is manifest in the infant fraction of a population through diseases or biological characteristics that are many times apparent at birth, sometimes of later development but directly attributable to parturition, and occasionally in disorders wholly remote from the birth process. Numerous morbid processes of women are related to age at which childbirth occurs and to numbers and elapsed interval of pregnancies. Observations on experimental animals suggest that maternal age effects occur in man under situations not yet investigated and in relation to diseases as yet unsuspected.

Information on maternal age and the obviously related variables of paternal age and birth rank is suggested as a useful addition to epidemiologic enquiries on specific diseases, especially chronic non-infective processes, even when no obvious connection is apparent between pregnancy or parturition and the particular inquiry. These items are also a desirable part of the medical record of patients in teaching hospitals and in clinics concerned with research.

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BOOK REVIEWS AND NOTICES

VIRAL AND RICKETTSIAL INFECTIONS OF MAN. Edited by THOMAS M. RIVERS, M.D., Director, Hospital of the Rockefeller Institute for Medical Research, 2nd ed. Pp. 719; 74 ills., 7 color plates. Philadelphia: J. B. Lippincott Co., 1952. Price, $7.50.

THE medical profession should welcome the second edition of this excellent work. It obviously fills a need for practical information on viral and rickettsial infections of man for the benefit of medical students and practicing physicians. The 30 contributors include the outstanding workers in this field, and at their head is Doctor Rivers who combines with his broad knowledge of the field an outstanding editorial talent. There is new material on Coxsackie virus, hemagglutination of viruses, interference between animal viruses, epidemic viral gastroenteritis, cat scratch disease, and salivary gland virus infections. The format is convenient. There are numerous excellent illustrations and 7 plates in color. There is an extensive bibliography. The work is heartily recommended. R. K.

DISEASES OF THE HEART AND ARTERIES. By GEORGE R. HERRMANN, M.D., Prof. of Medicine, Univ. of Texas. 4th ed. Pp. 652; 215 ills. and 4 color plates. St. Louis: C. V. Mosby Co., 1952. Price $12.50.

FOR a one volume book on cardiovascular disease, the author has packed in a lot of valuable and pertinent material. The book begins with a brief but complete discussion of cardiovascular embryology, physiology and diagnosis of heart disease. All phases of the subject are covered. Of particular excellence are two chapters covering electrocardiography which include the development of electrocardiographic theory and an excellent section on arrhythmias. All information is accompanied by clear and concise diagrams. Chapters on the classification of heart disease, congenital heart disease and chronic rheumatic heart disease are complete in their information. Hemodynamics as related to congenital heart disease and chronic rheumatic heart disease is included as well as a more specific section on normal values found from heart catheterization. There is one chapter on peripheral vascular disease which is brief in its content but proportional to the size of the book. All in all the reviewer feels this book is of definite value. G. M.

AN ATLAS OF SKULL ROENTGENOGRAMS. By BERNARD S. EPSTEIN, M.D. Associate Radiologist, The Jewish Hospital of Brooklyn, Brooklyn, New York and LEO M. DAVIDOFF, M.D., Neurosurgeon, Mount Sinai Hospital, and Director of Neurological Surgery, the Beth Israel Hospital, New York. Pp. 415; 603 ills. Philadelphia: Lea & Febiger, 1953. Price, $15.00.

THE Atlas of Skull Roentgenograms has succeeded in presenting a large number of excellent plates covering a wide variety of Roentgen pathology. The examples are not limited to single demonstrations but different manifestations of the same lesion have also been included. Along with the pathologic changes, examples of normal variation and variations of the skull at different ages are well documented.

As the title implies the text material has been reduced to a minimum. It is carefully chosen and well written. The plates are clear and expertly titled.

The emphasis is on plain film examination. No attempt is made to cover encephalography, ventriculography or cerebral angiography. The authors do point out the value of stereoscopic and planigraphic studies. The latter and special views (that is, tangential projections) are demonstrated in the book as adjuncts to the rountine examination.

The format and organization into chapters is logical and the text is clearly indexed making examples of specific Roentgen-ray pathological entities easy to find. It is an excellent book. A. A.

LIVER INJURY. Edited by F. W. HOFFBAUER, M.D,. Assoc. Prof. of Medicine, University of Minnesota. Pp. 265; 96 ills., 20 tables. New York: Josiah Macy, Jr. Foundation, 1953. Price, $4.00.

THIS book consists of the recorded transactions of the Eleventh Conference on Liver Injury, a meeting sponsored by the Josiah Macy, Jr. Foundation and attended by a specially invited group of clinicians and investigators interested in various phases of the anatomy, physiology, and pathology of the liver. The free and informal discussions that are a feature of these meetings are reproduced verbatim, thereby placing the reader in the same position as though he had

actually been privileged to be present during the deliberations. The topics considered at this conference were Infective Hepatitis, Enzyme Activity in Human Liver, Morphology of the Liver, Mechanism of Biliary Excretion in Mammals, and Hepatic Histochemistry. These subjects will be particularly attractive to those with a special interest in disease of the liver. The latter may also find stimulation for investigative work of their own in the ideas expressed and the experiences described by the conferees. For those who simply desire to become acquainted with current thinking in this field, this book may be recommended as a valuable reference.

J. B.

LONG-TERM DIABETES. By KNUD LUNDBAEK, M.D., Lecturer in Internal Medicine Aarhus University Medical School. Translated from the Danish by AXEL ANDERSEN, Copenhagen. Pp. 197; 33 ills., 25 tables. Copenhagen: Ejnar Munksgaard, 1953. Price, not given.

THIS volume consists of a remarkably detailed and thorough evaluation of a series of long-term diabetic patients studied in the municipality of Aarhus. There were 234 patients in whom the diabetic manifestations, their frequency, degree and correlations were tabulated, presenting a representative picture of the intrinsic composition of the long-term diabetic syndrome. The data, personally collected by the author, are supplemented by a review and discussion of the contemporary literature dealing with each phase of the problem. An extensive section on The Eye in Diabetes Mellitus was contributed by Dr. V. A. Jensen. This admirable book will be of great interest to all physicians engaged in the care of diabetic patients.

C. S.

CURRENT THERAPY, 1953. Edited by HOWARD F. CONN, M.D. Pp. 835. Philadelphia: W. B. Saunders Co., 1953. Price, $11.00.

THIS is the newest edition of a work intended to present the latest approved methods of treatment for the practicing physician. No less than 372 contributors have prepared sections for a book that is getting larger with each edition. In many instances, several contributors have been invited to give their preferred method of treatment for a given subject. This makes for a certain amount of duplication but at the same time gives a broader coverage and lets the reader exercise his own judgment. This book should find a wide appeal.

R. K.

FAMINE DISEASE IN GERMAN CONCENTRATION CAMPS. COMPLICATIONS AND SEQUELS. By PER HELWEG-LARSEN, HENRIK HOFFMEYER, JORGEN KIELER, EIGIL HESS THAYSEN, JORN HESS THAYSEN, PAUL THYGESEN, MUNKE HERTEL WULFF. Pp. 460; 25 ills. Copenhagen: Ejnar Munksgaard, 1952. Price, Dan. kr. 35.00.

THIS book is a careful study of the results of medical and social examination of 1,282 Danes who survived varying periods of internment in German concentration camps during World War II. There are chapters on hunger cachexia, hunger edema, polyuria, hunger, diarrhea, cardiovascular symptoms, metabolism, endocrine glands, avitaminoses incident to semi-starvation, mental disease, famine disease and its treatment and others. The incidence of tuberculosis as might be expected was high and was the most important cause of long periods of incapacity.

There is a chapter devoted to the symptoms of repatriation. In describing convalescence, the authors state that in a surprisingly short space of time the body weight and the appearance of most of the repatriates became normal. This led to a false conclusion that recovery had been complete. However, this did not mean that working efficiency had been regained. In spite of normal weight and appearance, there was restlessness, fatigue, and vegetative nervous symptoms.

Symptoms of compensation neurosis were found only in a few cases. The book contains a great amount of medical information and is an illuminating social study. There are 484 references.

O. E.

MEDICAL CLINICS OF NORTH AMERICA, MARCH, 1953. Nationwide Symposium on Nervous and Mental Diseases. Pp. 341; 54 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $15.00 per annum.

THIS issue is devoted to a symposium on the common organic diseases of the nervous system and those mental disturbances likely to be met by physicians in daily practice. Twenty-six authors have contributed 19 articles on various topics including neurological signs and symptoms and their interpretation and on the essentials of diagnosis and treatment of such conditions as convulsive disorders, acute purulent meningitis, tubercu-

lous meningitis, acute anterior poliomyelitis, the viral encephalomyelitides, the rickettsial diseases of the nervous system, acute intracranial vascular lesions, chronic subdural hematoma, ruptured lumbar disk, sciatica, multiple sclerosis, Parkinsonism, myasthenia gravis, progressive muscular dystrophy, behavior problems in children, acute psychotic episodes and chronic alcoholism. There is also an article on Erythroblastosis Fetalis. This is a very practical group of presentations and they are up to the usual high standard of excellence of this publication.

R. K.

PSYCHOSOMATIC RESEARCH. By ROY R. GRINKER, M.D., Clin. Prof. of Psychiatry, University of Illinois. Pp. 208. New York: W. W. Norton & Co., 1953. Price, $3.50.

AN attempt has been made to formulate a conceptual outline for problems in psychosomatic research. This book is general in character and does not specifically outline research techniques. It is, nevertheless, of interest to individuals who wish to engage in psychosomatic research. W. P.

MID-CENTURY PSYCHIATRY. Edited by ROY R. GRINKER, M.D. Pp. 183; 3 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $5.50.

THIS book represents the collection of several papers presented at the opening of the Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, Chicago, Illinois.

The editor, Dr. Grinker, says, "we plan to emphasize that clinical psychiatry as represented by study of the patient himself is only one small facet of the investigation of human behavior and its disorders. We are actually dealing with the science of behavior that takes into consideration part of total functions of healthy and sick human beings as they are influenced by interpersonal relations." Dr. Percival Bailey discusses the "Cortex and Mind" from an anatomical and evolutionary standpoint. Dr. Ralph W. Gerard discusses current neurophysiological concepts and their relation to behavior. Dr. George L. Engel takes up the defense mechanisms of the body as quantitative variables in a unitary concept of health and disease. Dr. David Shakow treats of the historical aspect of experimental psychology and discusses points of progress and obstruction in the field. Dr. Therese Benedek discusses the instinctual energies as compared with the energies which are constantly being produced and which influence the already constituted personality. Dr. H. S. Liddell makes a plea for determining the sources and uses of hopes and pleasures as well as focusing upon the problems of stress in disease.

Dr. David M. Levy presents data illustrating the methods of "Observational Psychiatry" as a technique. Dr. M. Ralph Kaufman recapitulates the recent developments within the field of Medicine which add to and extend psychoanalytic theory and practice. Dr. Thomas M. French and Dr. Franz Alexander discuss the therapeutic applications of psychoanalysis and its derivatives. Dr. Charles S. Johnson presents ways in which the social sciences have influenced psychiatry and a summary of the symposium is given by Dr. John P. Spiegel. O. E.

HORMONAL AND NEUROGENIC CARDIOVASCULAR DISORDERS. By WILHELM RAAB, M.D., Professor of Experimental Medicine and Head of Cardiovascular Research Unit, University of Vermont. Pp. 722; 108 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $15.00.

THIS is an interesting and important book. An effort has been made to point out the interrelations between Endocrinology and Cardio-angiology. There are three separate divisions, one being the experimental cardiovascular effects of hormones and neurohormones, the second being the cardiovascular features in endocrine and neuroendocrine syndromes and finally the section concerning endocrine and neuroendocrine factors in cardiovascular syndromes. This book will be of value to cardiologists, endocrinologists and internists. W. P.

ON BURNS. Edited by NATHAN A. WOMACK, M.D. Pp. 178; 7 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $5.50.

THIS book which stems from a civil defense symposium on burns should be read by all physicians who have to face the problem of the significantly burned patient. It presents an excellent example of the value of intelligent discussion in medical education. The multiple aspects of burn treatment and their related problems are presented clearly and succinctly.

The volume is of particular interest to surgeons and surgical residents. It is doubtful that the average medical student has the background necessary to obtain its full value.

The informality of this symposium has been retained and adds much to reader interest and enjoyment.

Dr. Womack and the members of this symposium are to be congratulated for an outstanding presentation of the various aspects of a vital medical problem. H. C.

THE ACQUISITION OF WORD MEANINGS: A DEVELOPMENTAL STUDY. By HEINZ WERNER and EDITH KAPLAN. Monographs of the Society for Research in Child Development, Inc., Vol. XV, Serial No. 51, No. 1, 1950. Child Development Publications, 1952. Price, not given.

STUDY reports an experimental investigation of the processes underlying the acquisition of word meanings through verbal contexts. It is an examination of many facets of such acquisition and symbolization, and the relating of these to developmental levels. The relationship of normal developmental personality changes to this acquisition is important. Findings include the changing process of generalization with age; increasing flexibility with age; further evidence for abrupt as well as gradual changes in mental development supporting the senior author's general position that "mental growth, rather than being conceived as a straight increase of achievement is here seen as a sequence of rises and declines of processes, subserving such achievement." Study is a contribution to the development of language behavior but will be of value primarily to those having a theoretical interest. W. M.

THE DISTRIBUTION OF SUBCUTANEOUS FAT IN CHILDHOOD AND ADOLESCENCE. By EARLE L. REYNOLDS. Pp. 189; 102 ills. Monographs of the Society for Research in Child Development, Inc., Vol. XV, Serial No. 50, No. 2, 1950. Child Development Publications, 1952. Price, not given.

THIS monograph is divided into three sections.

The first reviews the literature concerned with the study of adipose tissue and describes in detail the utilization of Roentgen-ray techniques to provide accurate measurements of subcutaneous fat.

The second section presents the measurement of subcutaneous fat determined by serial films of various soft tissue areas of 176 children in the Fell's group. These measurements are supplemented by those in a group of infants and young adults. The direct measurements are then correlated with age, sex, height, weight and developmental status separately and in groups with detailed statistical evaluation.

The third section is a group of descriptions of representative cases showing the extreme variation between "normal" individuals and the problem faced in the evaluation of any single child.

This study is exhaustive. It will be of interest primarily to students of growth and development. It will be of occasional value to the practitioner as a reference of normal ranges in evaluation of individual problems of subcutaneous adipose tissue in the child. The measurements help in evaluating the meaning of body weight in any child. There is an extensive bibliography. W. B.

THE LIFE AND TIMES OF SIR EDWIN CHADWICK. By S. E. FINER, Prof. of Political Institutions at the Univ. Coll. of North Staffordshire. Pp. 555; 3 ills. London: Methuen, 1952. (British Book Centre, Inc. New York, U. S. Agents.) Price $9.00.

THIS is both a timely and in several ways for medical men an important book about one of the leading figures in the field of public health. It is timely because of the remarkably rapid growth of this specialty in the English-speaking countries in the present generation and important because of the even greater significance of public health that can be visualized for the near future and because of the role played by Chadwick in pioneering this movement in England.

The subject matter of the book necessarily deals chiefly with such unglamorous topics as the Poor Laws, Factory Acts, Sanitation, Sewers, Nuisance Removal, Interment, Boards of Health, and Sanitary Engineering. Nor has the man himself an engaging personality to deal with: unbending, dogmatic, humorless, often intolerant, impatient, tactless, scheming and aggressive, yet churlish in defeat, it is small wonder that he was frequently the focus of controversy and abuse and went down to a personal defeat on the Board of Health Bill in 1856 that withdrew him from official life. From the 10 page bibliography, however, it is appar-

ent that his output of reports, addresses and pamphlets became greater than ever; continuing right up to 1890, the year of his death at the age of 90.

His public life reveals some instructive parallels with our situation in this country in the past decade. His ideal was that of his friend and teacher, Jeremy Bentham, "the greatest good for the greatest number." Admittedly a bureaucrat, he favored centralizing as much as possible in the State government, regarding the local representative boards as corrupt, inefficient and wasteful. When asked where centralization of power should stop, his ready but impractical answer was "where waste stops." Yet eventually the English ability for successful compromise brought about a good balance between local and central control of the health of the public. Can we do likewise?

Professor Finer's difficult task has resulted in a well documented record, if not always one that reads itself easily along. He has made good use of the copious hitherto unused material of several collections of private and public papers in producing this first full scale account of Chadwick's life and work. Finer points out that it was Chadwick who achieved the awakening of British statesmen to the duty of caring for the public health and of bringing it under the protection of Law, to quote Chadwick's successor, Sir John Simon, as well as stimulating them to many actual improvements. The pleasant side of Chadwick's personality is not neglected, such as his fondness for children and young people and for animals, and his courtesy and loyalty to those serving under him. This aspect is expanded in a character sketch (quoted in full) written in 1928 by his daughter, Marion, at the request of the director of the Chadwick Trust.

From the above picture, it should be obvious that this book will be far more valuable as a documented record than as another sympathetic biography of an important public servant. E. K.

MODERN TREATMENT. A GUIDE FOR GENERAL PRACTICE. Edited by AUSTIN SMITH, M.D., and PAUL L. WERMER, M.D. Pp. 1146; 13 ills. New York: Paul B. Hoeber, Inc., 1953. Price, $20.00.

THE rapid increase of medical knowledge makes it more and more desirable to put this vast material into convenient form for the practicing physician. This volume is an attempt to meet this need in the field of treatment. After introductory chapters on Patient-Physician Relationship, Pharmacological Principles in Treatment, Principles of Clinical Immunology, and others, there follow presentations on therapy not only in internal medicine but in various special fields such as surgery, obstetrics and gynecology, insofar as they apply to general practice. The emphasis is on treatment but, when necessary, there is adequate background and diagnostic material to orient the physician. The 53 authors who have participated in writing the book are all men with teaching experience. The book should find a wide and satisfactory appeal. R. K.

FAMILIAL NONREAGINIC FOOD ALLERGY. By ARTHUR F. COCA, M.D., Oradell, New Jersey. 3rd ed. Pp. 287; 26 ills. Springfield, Ill.: Charles C Thomas, 1953. Price $10.50.

THIS is the third edition of a monograph first published in 1942, in which Coca described a new method of diagnosis of food allergy, utilizing an increase in the pulse rate beyond 10 as the sole criterion. Because the reaction did not depend upon demonstrable antibodies, the syndrome was designated familial nonreaginic food allergy or idioblapsis. Any individual having this pulse-rate increase was regarded as food allergic and any symptom complex in which this was observed was attributed to idioblaptic allergy regardless of other etiologies. The present edition is an elaboration of the author's theory and experience with this method. It contains a simplified improved plan for pulse-testing single foods at 1 or ½ hour intervals throughout the day as well as chapters by various other contributors on the relationship of this type of food allergy to such conditions as glaucoma, multiple sclerosis, essential hypertension and low-grade infections including the common cold, as well as its value in the prevention of paralytic poliomyelitis and of dysmenorrhea, nausea and vomiting of pregnancy and similar conditions. Conclusions as to its value in these conditions are based solely upon relief obtained in extremely small numbers of patients in whom improvement followed removal of the offending food as determined by the pulse-rate method without the use of adequate controls or without regard for the possible occurrence of remission which sometimes occurs spontaneously in these diseases (for example, multiple sclerosis). One is struck by the ready explanations for the failure of the pulse-rate method; thus if the

pulse variation does not return to normal limits, it is attributed to allergy to too many foods, in which case, sympathectomy should be performed, or to sensitivity to inhalants like house dust, tobacco, or to the use of contaminating metal cooking utensils. Anyone with experience in the diagnosis of food allergy is well aware of the difficulties entailed when using only skin tests and trial diets. It was hoped, therefore, that this pulse-rate method would offer a new approach. However, instead of using it to help establish the importance of food allergy in known allergic conditions where such help is needed, as for example, migraine, urticaria, or gastrointestinal allergy, the author chose to demonstrate its etiological importance in many conditions of unknown etiology which formerly and for justifiable reasons were not considered allergic. This has deterred most allergists from using this method, although in justice to the author, it should be investigated by impartial judges. However, for those desiring to use the method, the present edition is recommended. L. T.

ACUTE RENAL FAILURE. By JOHN T. MACLEAN, M.D., Royal Victoria Hospital, Montreal. Pp. 120; 53 ills., 5 in color. Springfield, Ill.: Charles C Thomas, 1952. Price, $6.50.

IN this monograph, the author, a urologist, treats chiefly of the etiology, diagnosis and therapy of so-called lower nephron nephrosis. The author's qualification for this task appears to be his experience with the use of the artificial kidney in cases of anuria. Except for the portion of the monograph pertaining to artificial dialysis, the coverage of the topic is inferior to that present in many recent internal medicine texts.

Unfortunately, the treatise was apparently prepared prior to the publication of Jean Oliver's monograph on the lesions of "lower nephron nephrosis." Thus one of the most significant contributions to the field is omitted.

Aside from errors of omission, several errors of commission are also present in the reviewer's opinion. On page 22, the electrocardiogram shown seems to be a poor illustration of hyperkalemia and resembles more closely the electrocardiogram of hypocalcemia. On page 67, the administration of sodium chloride is interdicted in anuria but the use of sodium bicarbonate or sodium lactate is advised for the attendant acidosis without any warning of its possible dangers.

The statement that "ACTH may eliminate both the outward evidence of the disease, and the disease process itself" and the recital of a case of anuria which responded while receiving cortisone, places unwarranted confidence in these agents, agents which may well be contraindicated under the circumstances.

The author wisely concludes that it is difficult to know if the artifical kidney is truly life-saving. He feels that it has tided some patients over critical periods of acute anuria. W. S.

THE PRINCIPLES AND PRACTICE OF MEDICINE. By L. S. P. DAVIDSON, B.A. CANTAB., M.D., Professor of Medicine and Clinical Medicine, University of Edinburgh. Pp. 919; 57 ills. Edinburgh: E. & S. Livingstone, Ltd., 1952; Baltimore: Williams & Wilkins Co., 1952. Price, $6.75.

ALTHOUGH the subtitle calls this "a textbook for students and doctors," it is simply a compilation of lecture notes as delivered to students in the University of Edinburgh by the Professor of Medicine and thirteen other members of his staff. The coverage of many subjects is thin and in not a few instances very inadequate. Names and sources are rarely mentioned. Although the book might be helpful to the students of this medical school, it cannot be recommended as a text of general usefulness. R. K.

PHYSICS AND MEDICINE OF THE UPPER ATMOSPHERE. A STUDY OF THE AEROPAUSE. By CLAYTON S. WHITE, M.D., Director of Research, Lovelace Foundation for Medical Education and Research, and OTIS O. BENSON, JR., BRIGADIER GENERAL, USAF (MC), Commandant, USAF School of Aviation Medicine. Pp. 611; 196 ills. Albuquerque: University of New Mexico Press, 1952. Price, $10.00.

IN November, 1951, there was held at San Antonio, Texas, under the sponsorship of the Air University School of Aviation Medicine a Symposium on the Physics and Medicine of the Upper Atmosphere. The Lovelace Foundation for Medical Education and Research has made possible the publication of the contributions of 38 contributors, including leading scientists representing many disciplines, institutions of learning and research, and the Armed Services. The coupling of the terms "Physics" and "Medicine" in the title is significant of their

inseparability in planning the machines that are to carry man farther and farther above the earth's surface, and some day into outer space. Here is indeed a preview of a new era. R. K.

MEDICAL CLINICS OF NORTH AMERICA. BOSTON NUMBER, SEPTEMBER, 1952. Pp. 320; 31 ills. Philadelphia: W. B. Saunders Co., 1952. Price, $15.00 per annum.

THIS Boston number is devoted to a symposium on Specific Methods of Treatment. There are articles on the treatment of burns, the emergency management of chemical burns of the eye, the use of vitamin B_{12} in medicine, the antibiotic treatment of viral diseases, the treatment of pulmonary tuberculosis, bronchial asthma, laryngotracheal bronchitis, thrombo-embolism, peptic ulcer, hepatitis, motion sickness, and a dozen other important topics. The wide range of practical subjects discussed will make this a particularly acceptable article to clinicians. R. K.

FUNCTIONAL ENDOCRINOLOGY FROM BIRTH THROUGH ADOLESCENCE. BY NATHAN B. TALBOT, EDNA H. SOBEL, JANET W. MCARTHUR AND JOHN D. CRAWFORD, Harvard University Medical School. A Commonwealth Fund Book. Boston: Harvard University Press, 1952. Price, $10.00.

THIS is a complete and unqualifiedly illuminating analysis of the functions and dysfunctions of the endocrine glands throughout the childhood period. The word analysis is used advisedly, because of the thorough manner in which all phases of the endocrines have been gone into. The active principles of each gland are presented from the viewpoints of sites of production, physiologic activities, interrelations with homeostatic mechanisms and other hormones, clinical phenomena associated with hypo- and hyperfunction, laboratory and metabolic approaches to the investigation of disturbances, therapeutic substances and dosages, and related pertinent facets of modern endocrinology. The style is readable, the information authoritative, the illustrations and diagrams numerous and lucid, and the typographic arrangements a delight to the eye. Most of the case reports and tables of laboratory data are from the authors' own rich experience.

Apart from a few reservations with respect to admittedly dogmatic statements regarding some minor points, the only major omission from an otherwise comprehensive set of presentations is the paucity of section pictures of the glands in disease states. These will probably not be missed except by those interested in the histopathologic correlations between morphologic and functional disturbances. An exception is to be found in the testis chapter, in which are reproduced a number of biopsy sections of normal and abnormal tubular and interstitial cell patterns.

Pediatricians, clinicians, endocrinologists and all other physicians who wish a thorough insight into the normal workings of the endocrine glands and the practical problems of the endocrinopathies will find this textbook eminently rewarding. I. W.

NEW BOOKS

The Psychopathic Delinquent and Criminal. By GEORGE N. THOMPSON, M.D., Assoc. Clin. Prof. of Neurology and Psychiatry, University of Southern California. Pp. 161; 29 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $4.50.

THIS book is one of the many that deal with personality problems which are baffling to both law and psychiatry. The author leans heavily upon the theory that delinquency is due to hereditary defect or brain damage. He says "Psychological factors affecting the individual in a psychodynamic way seem to have little to do with the etiology of delinquency in the true psychopath." However, in order not to discard entirely the evidence presented by workers in the psychogenic field he says, "The syndrome of psychopathic personality develops upon the basis of psychogenic factors working upon a previously injured brain." Evidence that the brains of psychopaths have been damaged is not conclusive. The bibliography has only sketchy references to work that has been done by able people representing the sociological-psychological factors in this condition. At best this is an incomplete treatise on a very complex area of human behavior. O. E.

Virus and Rickettsial Classification and Nomenclature. Edited by ROY WALDO MINER. Pp. 242; 24 ills. New York: New York Academy of Sciences, 1953. Price, $4.00.

Rapid Chemical Micromethods for the Analytic Fractionation of Serum Proteins. By WILLIAM Q. WOLFSON, M.D., and CLARENCE COHN, M.D. Pp. 15. Ann Arbor: The Overbeck Co., 1953. Price, $1.00.